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Renal Function, Cardiovascular Disease and Long Term Outcome in Different Cohorts of the Glasgow Population

by

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A thesis submitted for the degree of Doctor of Medicine in the Department of Clinical Medicine, Trinity College, University of Dublin

2011

DECLARATION:

I declare that this thesis has not been previously submitted for a higher degree.

I declare that this thesis is entirely my own work, including collection of data, study design, data analysis and preparation of the manuscript. The original screening visits performed over fifteen years ago in the Clinical Research Initiative were designed and directed by my supervisor, Professor Henry Dargie; persons employed by the Clinical Research Initiative at that time performed the investigations. Biochemical analysis of blood samples was facilitated by Dr JJ Morton (University of Glasgow) and Dr R Spooner (Gartnavel Hospital, Glasgow).

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Aengus Murphy

March 2011

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This thesis incorporates data collected from over 3000 individuals from the Glasgow area who willingly gave up their time to attend for screening visits, many of whom did so on more than one occasion. Without their effort and altruism, this thesis could never have been produced.

I very much appreciated the support, advice and company of my colleagues employed in cardiac research at the Western Infirmary during my time there.

I dedicate this thesis to Grace, my wife, and to Lucan, my son.

Aengus Murphy
March 2011

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ACE	angiotensin converting enzyme
ACM	all cause mortality
ACS	acute coronary syndrome
AF	atrial fibrillation
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blocker
BNP	brain natriuretic peptide
BMI	body mass index
BSA	body surface area
BSE	British Society of Echocardiography
CABG	coronary artery bypass grafting
CKD	chronic kidney disease
CrCl	creatinine clearance
CRI	Clinical Research Initiative
CRT	cardiac resynchronisation therapy
CVS	cardiovascular
Δ	delta (change in)
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
ESRF	end stage renal failure
GFR	glomerular filtration rate
GP	general practitioner
HF	heart failure
HR	hazard ratio
HTN	hypertension
ICD	implantable cardiac defibrillator
IHD	ischaemic heart disease
IQR	inter-quartile range
LV	left ventricle

LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVDD	left ventricular diastolic diameter
LVSD	left ventricular systolic dysfunction
MI	myocardial infarction
MONICA	monitoring of trends and determinants in cardiovascular disease
NHANES	National Health and Nutrition Examination Survey
NSTEMI	non-ST-elevation myocardial infarction
NT-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
PCI	percutaneous coronary intervention
RAAS	renin-angiotensin-aldosterone system
RI	renal impairment
ROC	receiver operator characteristic
SD	standard deviation
STEMI	ST-elevation myocardial infarction

SUMMARY

Over the past ten to fifteen years, the interaction between cardiovascular disease and chronic kidney disease (CKD) has come under increased scrutiny. Traditional cardiovascular risk factors are also associated with the onset of kidney disease whilst even milder forms of renal disease have been shown to independently predict adverse outcome in a number of different populations, particularly cardiovascular death. Over the past 5 years, change in renal function over time has been increasingly studied in an attempt to further understand cardio-renal interaction.

Scotland has the worst cardiovascular morbidity and mortality within the United Kingdom. The Clinical Research Initiative (based in the Western Infirmary, Glasgow) undertook studies of different cohorts of the Glasgow population in the 1990s, screening a large number of individuals by means of medical history, echocardiography and blood sampling. Stored blood samples were defrosted in 2006 and serum creatinine analysis performed. eGFR was calcluated with the MDRD formula. All deaths up the end of 2006 were collated from the Scottish Registry office. This thesis sought to examine whether milder forms of renal impairment was independently predictive of outcome in three different Glasgow cohorts.

Results: POST MI cohort: 924 patients who had sustained an index myocardial infarction (MI) in the preceeding 2-11 years underwent screening in 1995. 17.6% of these individuals had an eGFR of less than 60ml/min/1.73m^2, and these were more likely to be elderly and female. 16.9% had renal impairment based on serum creatinine levels (>106μmol/l), but this method appeared to misclassify elderly women as having normal renal function, when they actually had reduced eGFR. During the11.0 ± 0.4 years of follow up, 302 individuals died, of which 197 were cardiovascular deaths. eGFR and CKD classification were univariate but not independent predictors of all cause mortality and cardiovascular disease. Renal impairment, based on serum creatinine was independently predictive of all cause mortality and cardiovascular disease (respective adjusted HRs 1.40 [1.03 – 1.90] and 1.46 [1.01 – 2.13]. POST MI rescreen: 500 individuals who attended the original 1995 screening returned for a further screening visit in 1998. Of these, 123 had died by the end of 2006, of which 85 were cardiovascular deaths. Change in (Δ) both eGFR and serum creatinine were both normally distributed with a mean change of -1.91 ± 9.47 ml/min/1.73m^2 and +1.65 ± 12.1 μmol/l respectively. Δ eGFR and Δ creatinine were both independently predictive of adverse

outcome. The tertile with the largest fall in eGFR had adjusted HRs of 1.66 (1.01 – 2.71) and 1.84 (1.01 – 3.36) for all cause mortality and cardiovascular death respectively. Worsening renal function (rise in creatinine >26.8μmol/l) was only seen in 17 individuals but was strongly predictive of adverse outcome. GP-Heart Failure cohort: This incorporated 500 individuals from primary care who were taking HF therapies, who underwent screening in 1996. Only 199 individuals were found to fulfil a diagnosis of HF. 38.6% had an eGFR <60 ml/min/1.73m^2, whilst 58.6% had renal impairment based on serum creatinine (>88.4μmol/l). By the end of 2006, 224 individuals had died. Individuals with HF alone had very similar outcomes to those with CKD alone. eGFR and CKD classification were univariate but not multivariate predictors of outcome. Compared to the highest eGFR quartile, the lowest quartile was independently predictive of cardiovascular death [HR 2.35 (1.04 – 5.34)] and almost predictive of all cause mortality [1.79 (0.98 – 3.25)]. Moderate to severe renal impairment based on serum creatinine was independently predictive of both all cause mortality and cardiovascular death. MONICA cohort: This involved members of the general population who were screened in 1992 and again in 1996. 851 individuals were included in the analysis, of which 109 had died by the end of 2006. 101 had eGFR < 60ml/min/1.73m^2 and this was a univariate but not multivariate predictor of outcome. Age and gender matched renal impairment based on serum creatinine (>109.6 μmol/l in men, > 97.0μmol/l in women) was a univariate predictor of outcome only. Framingham criteria for renal impairment (>136μmol/l in men, >120μmol/l in women) was an independent predictor of adverse outcome.

Conclusion: Mild forms of renal impairment are independently predictive of poor long term outcome in different cohorts of the Glasgow population. However, different methods of defining renal impairment are required for each cohort. Additionally, chronic change in renal function following MI is predictive of long term prognosis.

CHAPTER 1

INTRODUCTION

1.1 Introduction

It is becoming increasingly difficult to view cardiovascular disease and chronic kidney disease (CKD) as clinically separate entities. Both disease processes are strongly influenced by the same disorders, that is, hypertension and diabetes mellitus (DM), whilst other traditional cardiovascular risk factors such as dyslipidaemia and smoking are also independently associated with the development of kidney disease. Atherosclerotic disease of the renal arterial tree is now thought to be increasingly responsible for end-stage kidney disease, particularly in the elderly. Furthermore, it is now recognised that cardiovascular disease and kidney disease, if not already co-existing, are likely to initiate and exacerbate the development of the other, usually resulting in adverse outcomes for patients; this unfavourable interaction is most evident in extreme scenarios such as end stage kidney disease or chronic congestive heart failure (HF).

Kidney disease is common in patients with cardiovascular disease and it is now evident that even mild forms of renal impairment carry poorer prognosis and are particularly associated with cardiovascular death. Cardiovascular disease itself leads to progressive renal impairment, therefore completing a viscous cycle. Thus, cardiorenal interaction via hormonal, metabolic and haemodynamic pathways accelerates pathophysiology in both the heart and kidney, leading to increased human and financial costs.

This thesis aims to examine the evidence of cardiorenal interaction in the general population and also in those with established cardiovascular disease. The prevalence, cause and demographics of renal impairment in different cohorts of the Glasgow population will be studied, and its influence on long term outcome will be quantified.

1.2 Epidemiology of cardiovascular disease

Despite advances in recognition, diagnosis and treatment, cardiovascular disease continues to inflict a large burden on the population of most Western countries. It has been estimated that in the United Kingdom in 2008, 123 000 persons under the age of 75 years will have sustained a myocardial infarction (1), with the overall number much higher if older patients are included (2). In the United States, it's thought that there were over one million myocardial infarctions in 2008, of which almost two thirds were an index MI (3).

Left ventricular systolic dysfunction (LVSD), usually as a result of coronary artery disease, has been shown to be present in 2.9% of the Glasgow population aged between 25 and 75 years; only approximately half of these individuals are symptomatic, that is, have HF (4). A similar study in the West Midlands of England found that 1.8% of people aged over 45 years had an ejection fraction below 40%, again with only half exhibiting symptoms (5). The prevalence of LVSD increases with age, with 6.8% of 75 year olds fulfilling ECHO criteria for this (4-6).

HF is becoming increasingly frequent as the treatment of myocardial infarction (MI), LVSD and HF itself improves. The incidence of new HF diagnosis in Britain has been reported as 1.3 per 1000 population per year for those aged over 25 years, rising to 11.6 per 1000 population per year for those aged over 85 years (7). It is estimated that in Scotland, there are currently 40 000 men and 45 000 women living with heart failure, and this number is expected to increase by 17-31% by 2020 (8), simply as a result of increasing population alone.

Cardiovascular disease causes 198,000 deaths in the UK each year and remains the leading cause of premature death in the UK, being responsible for 25% of deaths in persons aged less than 75 years old. Coronary heart disease is the main cause of cardiovascular death, causing 94000 deaths per year in the UK; one fifth of men and one seventh of women will die as a consequence of coronary artery disease (1).

In Scotland, there is evidence that survival rates have improved over the past two decades following MI (9) and also for patients with HF (10). Despite this, Scotland has the highest rate of coronary heart disease in the United Kingdom, along with the North of England, followed by Northern Ireland (1). Compared to the south west of England, the rate of premature cardiovascular death in Scotland is 64% higher in men, and 100% higher in women. In addition to the human cost, cardiovascular disease exerts a considerable drain on government budgets. It is estimated that almost £15 billion was spent in 2006 in the UK treating cardiovascular disease, of which 75% is spent within hospitals (1,11).

1.3 Measurement of renal function

Before examining any relationship between cardiovascular disease and kidney disease, it is important to understand the methods by which renal function is measured. The function of the kidneys is defined as the glomerular filtration rate (GFR); this is the combined total volume of plasma ultrafiltrated across the glomerular capillary basement membrane per minute in every individual glomerulus, of which an average human will have 10 to 20 million.

Direct accurate measurement of the GFR is not possible; instead, indirect methods have been developed. The use of a "perfect filtration marker" allows indirect measurement of

calculating the GFR, that is, a chemical that is freely filtered by the glomerulus, not protein bound and not metabolised, secreted or absorbed by the kidney. Measurement of the clearance of this chemical would therefore be equal to the GFR and is calculated by the following formula:

$$C(x) = U(x)\ V / P(x)$$

where C(x) is the renal clearance of substance x, U(x) is the urinary concentration of substance x, V is the urine flow rate and P(x) is the serum concentration of substance x (12).

Inulin, a naturally occurring polysaccharide found in plants but not humans, is one such perfect filtration marker (13) and inulin clearance is widely accepted as the gold standard method of assessing GFR. Mean GFR, using inulin clearance, in a healthy man under 30 years old is approximately 130 ml/min/1.73m^2 body surface area, and approximately 120 ml/min/1.73m^2 in a healthy woman of the same age (14). However, using inulin in humans requires intravenous administration and its use in clinical medicine is impractical. Instead, creatinine has become widely used as a marker of renal function; this chemical is produced in the body by nonenzymatic dehydration of creatinine, which is found predominantly in skeletal muscle. It is excreted from the body almost exclusively through the kidneys, although bacterial degradation of creatinine does occur in the gut when serum creatinine levels are very high (15).Creatinine fulfils some of the requirements of being a perfect filtration marker, but not all. A proportion of creatinine is actively secreted from the proximal tubule, and in states of low urine flow such as dehydration or decompensated heart failure, tubular reabsorption of creatinine can occur (12).

Although the renal clearance of creatinine would be the more accurate measurement of renal function, serum creatinine concentration has become widely used as a more convenient method of assessing renal function. This is based on the premise that as renal function deteriorates, creatinine clearance (CrCl) will fall and thus serum creatinine will rise.

The most widely used method of measuring creatinine levels is the Jaffé method(16), first described in the nineteenth century; creatinine reacts directly with picrate ion under alkaline conditions to form a red-orange colour which is easily quantified as either μmol/l or mg/dl. Its major drawback is that up to 20% of the colour produced is due to non-creatinine substances such as glucose, uric acid and ascorbic acid. Another problem is that high serum bilirubin levels interfere with the Jaffe reaction and thus this cannot be used in very jaundiced patients. Despite this, the Jaffe method is still a much more popular method of creatinine analysis than the alternative methods, for example, the kinetic picrate alkaline method, Ecktachem method or creatinine PAP method.

The inaccuracy of using serum creatinine as a marker of renal function is usually acceptable for clinical purposes but it is important to recognise a number of points. Firstly, serum creatinine concentration will be influenced by muscle mass, given that this is where it is derived. Increased muscle mass following sustained physical training would lead to higher serum creatinine levels, which may be misinterpreted as worsening renal function. The converse is more concerning, whereby a chronically ill patient with cachexia and muscle loss may have co-existent progressive renal impairment being masked by a static creatinine level. Ingestion of meat is an alternative source of creatinine and therefore extreme eating habits, either carnivorous or vegetarian, could also affect CrCl (17)

1.3.1 Cockcroft and Gault equation

As already stated, the renal clearance of creatinine is the more accurate assessment of GFR. This is sometimes calculated using serum creatinine and by collecting urine over a prolonged period, usually 24 hours. However, the accuracy of urine collection is usually unreliable, particularly in ill or elderly patients. A number of equations have been designed to estimate CrCl using serum creatinine concentration and other easily measured variables. The most popular method is that designed in the 1970's by Cockcroft and Gault (18) who derived a simple equation whereby creatinine clearance could be calculated using serum creatinine, age, weight and gender:

$$CrCl = \frac{[140 - \text{age (years)}] \times [\text{mass (kg)}] \times [0.85 \text{ if female}]}{\text{serum creatinine (in mg/dl)} \times 72}$$

This equation was derived from studying approximately 250 healthy individuals, of which only ten were female. This method seems to overestimate GFR at lower levels (19) (where accuracy is perhaps at its most important) and has not been validated in ill populations. Calculated CrCl proved to be popular method of quantifying renal failure for many years, usually dividing patients based on 30 point increments of CrCl.

1.3.2 MDRD formula and CKD classification

In 1999, a new method of calculated an estimated GFR (eGFR) was published (20). In a study of over 1600 patients and using stepwise regression, the Modification of Diet in Renal Disease (MDRD) formula was designed where eGFR could be calculated using six variables:

$$eGFR = 170 \times \text{creatinine (mg/dl)}^{-0.999} \times \text{age}^{-0.176} \times \text{urea nitrogen (mg/dl)}^{-0.170} \times \text{albumin (g/dl)}^{+0.318} \text{ (x 0.762 if female) x (1.180 if black)}$$

This has since been simplified to a 4 variable MDRD formula, which is now in widespread use:

$$eGFR = 186 \times creat\ (mg/dl)^{-1.154} \times age^{-0.203}\ (\times 1.21 \text{ if black})\ (\times 0.742 \text{ if female})$$

or

$$eGFR = 32788 \times creat(\mu mol/l)^{-1.154} \times age^{-0.203}\ (\times 1.21 \text{ if black})\ (\times 0.742 \text{ if female})$$

This formula has since been validated in a number of populations including the general population (21) and in those with advanced renal failure (22) although some report that the MDRD formula is less accurate when GFR is normal or raised (23).

The widespread adoption of using eGFR as a standard measure of renal function has allowed simplification of defining which patients have renal disease. Using serum creatinine alone proved problematic to apply to large populations and different studies would use differing cut-offs of creatinine concentration as definition of renal impairment; usual practice would be to use relatively high creatinine cut-off levels but this would lead to a number of patients, usually elderly or female, with low GFRs being defined as having normal renal function.

In 2002, guidelines (24) were published where chronic kidney disease (CKD) stage could de defined based on eGFR. These are summarised thus:

CKD stage 1: Normal or relatively high GFR (>90 ml/min/1.73m^2) and evidence of kidney disease (proteinuria, haematuria, abnormal renal imaging)

CKD stage 2: Mild reduction in GFR (60 - 89 ml/min/1.73m^2) and evidence of kidney disease (proteinuria, haematuria, abnormal renal imaging)

CKD stage 3: Moderate reduction in GFR (30-59 ml/min/1.73m^2)

CKD stage 4: Severe reduction in GFR (15 – 29 ml/min/1.73m²)

CKD stage 5: Established kidney failure (eGFR < 15ml/min/1.73m²) or permanent renal replacement therapy.

Anyone with a GFR of less than 60ml/min/1.73m² for more than three months is classified as having CKD, irrespective of the absence of any other evidence of kidney disease. Current British Guidelines sub-divide stage 3 CKD in to stage 3A (GFR 45 – 59 ml/min/1.73m²) and stage 3B (GFR 30 - 44 ml/min/1.73m²) for screening and referral purposes (25).

1.4 Epidemiology of renal failure

Examining the epidemiology of renal impairment is made more difficult as the methods of measuring renal function, and therefore defining renal impairment, have developed over time. For example, the prevalence of chronic renal disease is almost doubled if the Cockcroft-Gault method (CrCl) is used when compared to the MDRD formula (eGFR) (26).

1.4.1 Epidemiology of end-stage kidney disease

The most extreme form of CKD is end-stage renal failure, where the kidneys can no longer control fluid status, electrolyte concentrations and acid-base regulation. Without treatment, it is uniformly and rapidly fatal. Where renal transplantation is not available, the treatment options for renal replacement therapy are peritoneal dialysis or haemodialysis.

In the United States, the number of patients on haemodialysis or peritoneal dialysis in 2004 was 335963, representing 0.1% of the population; approximately one-third of these individuals had started dialysis that year (27). In the United Kingdom, in 2005, 22702

individuals were on receiving renal replacement therapy (three quarters on haemodialysis), about one third the rate of the US (28). In the same years, there were 136136 individuals living with a renal transplant in the US, compared to 19074 in Great Britain- approximately 50% more prevalent in the US (27,28).

1.4.2 Prevalence of CKD in general population

Using the MDRD method as gold standard and the most recent published guidelines (24) on definition of CKD, the full extent of renal disease in the general population is now becoming apparent. In the United States, 11 to 13% of the population aged over 20 years have evidence of CKD, with 4.7% having stage 3 CKD or worse (29,30); this corresponds to 8,300,000 individuals. In those aged over 65 years old, 11.0% have stage 3 CKD or worse. This figure is comparable to studies performed in general populations in Europe, Asia and Australia (31) where the median prevalence of CKD stage 3 or worse was 7.2% in those aged over 30 years old. The burden of CKD is thus considerable and evidence indicates the problem is increasing (32,33) as the population gets increasingly elderly, at least in the developed world.

Increasing age is a strong predictor of CKD (34), and the prevalence in those aged over 64 years old can be as high as 35.8% (31). Women have a lower GFR than men; given that the same cut-off of 60 ml/min/1.73m^2 is applied to both genders, it is not a surprise to find that females constitute the majority of individuals with CKD (31). In the US, women are 50% more likely to have CKD than men although some report up to a three folds increased risk of CKD in women (29,35). Thus, an argument could be made that age and gender matched eGFR criteria be developed for the definition of CKD (36,37).

1.4.3 Prevalence of CKD in CVS disease

The prevalence of CKD in populations with established cardiovascular disease is considerably higher than that seen in the general population. This is due in part to the confounding issue of age, but also due to the high prevalence of cardiovascular risk factors such as hypertension and DM.

Once again, the prevalence of renal disease is influenced by whichever measure of renal function is utilised. Recent post MI drug trials have reported approximately one third of individuals having stage 3 CKD or worse (38-40) although advanced renal failure is usually an exclusion criteria for entry to these trials. Registry or observational studies following MI report 12.6% to 41% of individuals having eGFR < 60ml/min/1.73m^2(41,42) but other studies that used CrCl < 60 as a definition of renal impairment varied from 14.5 to 35%(43-45).

Cohorts with HF have an even higher rate of renal disease, probably as a reflection of older age and more advanced cardiac disease. One third to one half of patients with HF will have eGFR < 60ml/min/1.73m^2 (46-48) with a similar proportion having CrCl < 60 (49,50).

1.5 Causes of chronic renal disease

In medical textbooks, the lists of chronic kidney disease aetiology include a variety of unusual disorders such as glomerulonephritidies, IgA nephropathy, adult polycystic kidney disease and tubular nephritis to name a few. However, by far the most common cause of kidney disease is DM, being responsible for almost 50% of new patients starting renal replacement therapy (27). Diabetic nephropathy is characterised by proteinuria, which usually precedes reduced kidney function; the pathophysiology includes thickening of the glomerular

and tubular basement membranes, leading to mesangial expansion and reduced glomerular filtration surface. This glomerulosclerosis can be focal or diffuse and actually produces hyperfiltration of the glomerulus in the early stages. This form of nephropathy is usually most evident in type 1 diabetics; a more heterogeneous picture is seen in type 2 diabetics who are generally older and have other co-morbidities influencing kidney damage (51).

The second most common cause of irreversible kidney disease is hypertension (27). Originally, hypertensive nephropathy was divided into benign (hyaline arteriosclerosis leading to focal ischaemic glomerular obscelence and nephron loss) and malignant (acute disruption of vasculature and glomeruli with necrosis and thrombosis) processes (52). However, it is now recognised that there is a spectrum of renal damage attributable to hypertension. Furthermore, hypertension is rarely the sole culprit and is recognised as a contributing factor in the progression of most other forms of chronic kidney disease, particularly diabetic nephropathy.

In addition to hypertension and DM, it seems that other conventional risk factors for cardiovascular disease are also associated with the development of kidney failure. One long term study over 18 years of patients with normal renal function, as expected, identified DM and hypertension as strongly predictive of developing new onset kidney disease (53); however, smoking, low HDL cholesterol and raised BMI were also predictive of new onset kidney disease(53). Indeed, the presence of cardiovascular disease (including coronary, cerebrovascular and peripheral vascular disease) is also associated with progressive kidney disease, independently of hypertension and DM (54). It is also recognised that old age and male gender are strong predictors of developing kidney disease (34,53-55).

All of this suggests that atherosclerosis may play a large role in the progression of kidney disease, irrespective of the primary cause. This is likely to involve small and medium sized renal vessels as well as larger arteries (in the form of renal artery stenosis). There is little observational evidence to support this theory however but it is postulated that atherosclerotic renovascular disease is increasingly responsible for the development of advanced kidney disease, particularly in the elderly (27,32,33).

1.6 CKD and CVS disease and outcome

As discussed, patients with cardiovascular disease have high rates of CKD; conversely, patients with CKD have higher rates of cardiovascular disease. This is most evident in the ESRF population where the mechanism of death is more likely to be due to a cardiovascular cause than to any other.

The rates of established cardiovascular disease in ESRF is staggering; LV hypertrophy is almost universal and 15% have LVSD (56,57). The prevalence of clinically evident IHD is 40%, with a similar percentage having clinical HF (58); this is similar regardless of the method of renal replacement therapy. As well as being more likely to suffer a MI, the ESRF population have a much poorer prognosis after index MI compared to similar non-dialysis patients (59). ESRF also confers poorer prognosis following de novo HF (60).

Even when adjusted for age, gender and other major co-morbidities, ESRF carries a 5 –fold increased risk of cardiovascular death; unfortunately, dialysis patients also have a higher rate of non-cardiovascular death (61). Sudden cardiac death accounts for one quarter of all deaths in ESRF, with an estimated annual rate of 7% (62).

Even patients with renal transplants carry a cardiovascular burden 3 to 5 times that of the general population(63); 50-70% have LV hypertrophy and 15 % have coronary artery disease(57,64). One third to one half die a cardiovascular death (57,65), at twice the rate of the general population.

As demonstrated, severe renal disease carries a particularly poor cardiovascular prognosis. However, it is now apparent that even less severe forms of renal disease are associated with cardiovascular death- indeed, patients with CKD are more likely to die a cardiovascular death than to progress to ESKD (66). Studies largely performed in the early part of this century have identified that mild and moderate renal impairment is independently associated with increased mortality and cardiovascular death in particular. This has been demonstrated in both the general population (67-75) but also in populations with established cardiovascular disease (38,39,41-43,45-50,71,76-92). These studies are discussed in more detail below. Thus, it is now widely accepted that renal disease and cardiac disease often co-exist, interacting with and aggravating the other; this usually leads to poorer long term outcome for patients which in turn increases demand on medical services and government budgets.

1.6.1 CKD and outcome in general population

A number of studies have addressed long term outcome in the general population, looking specifically at the influence of mild or moderate kidney disease; these are summarised in Table 1.1.

	n	Patient characteristics; mean age (years)	Prevalence of renal impairment	Risk associated with RI
Culleton et al 1999 (67)	6233	28-65 years old, general population; 54	8.7% male and 8.0% female with mild RI	Male: ACM OR 1.31 for RI, Female no significant association
Garg et al 2002 (93)	2352	General population, 25-74 years old; -	9.4% with moderate RI	Moderate RI not independently predictive of ACM or CVS death
Meisenger et al 2006 (68)	7543	General population, 45-74 years old; 58	16.4% eGFR < 60	No independent association with ACM. Male adjusted OR CVS 1.48, female OR CVS 1.60
Fried et al 1998 (69)	5201	General population aged >65; 73		ACM 1.71 Cr > 130 v Cr < 80
Henry et al 2002 (243)	631	General population 50-75 years; 64	Mean eGFR 67.8	ACM 1.15, CVS 1.26 per SD fall in eGFR
Muntner et al 2002 (70)	6384	General population 17-74 years; 50	5% eGFR < 70ml	CVS death CVS 1.51 eGFR < 70 v >90
Go et al 2004 (71)	1120295	>20 years old, integrated health community; 52	17.5 % eGFR < 60	HR ACM 1.2 eGFR 45-60 v > 60
Wattanakit et al 2006 (72)	12243	General population, 45-64 years; 54	2.2% eGFR <60	CVS death CKD 3.4/1000 years v no CKD 1/1000
Manjunath et al 2003 (73)	15360	Community, 45-64 years; 54	2.9% eGFR < 60	HR 1.38 for MACE eGFR < 60 v > 60
Rotterdam study 2005(74)	4484	Healthy population; 70		OR MI 1.90 lowest eGFR quartile v highest
McCullough et al 2008 (75)	31417	Community, male 18-55 years, female 18-65 years; 45	10.8% eGFR <60	Premature CVD/MI OR 1.44 for CKD

Table 1.1 Epidemiological studies assessing mild to moderate renal disease and outcome in the general population
[RI, renal impairment; ACM, all cause mortality; CVS, cardiovascular; OR, odds ratio; HR, hazard ratio; Cr, creatinine]

The earlier studies were inconclusive regarding whether milder renal impairment was independently associated with adverse outcome (67,69,93)- these studies were similar in that they used serum creatinine cut-offs as definitions of renal impairment. Analysis of the Framingham cohort in 1999 concluded that mild renal impairment was independently predictive of all cause mortality in men but not women (67). Further to this, NHANES data (93) published 3 years later concluded that even moderate renal impairment was not independently predictive of outcome in any gender. As early as 1998, Fried et al had

indicated that a serum creatinine over 130 μmol/l carried an adjusted HR of 1.71 for death at 5 years compared to creatinine below 80 μmol/l (69).

The adoption of the MDRD formula and eGFR estimation coincided with new evidence indicating that mild chronic kidney disease did carry increased risk in the general population, particularly of cardiovascular death. A very large study in the United States involving over one million members of the general population indicated that CKD stage 3 or worse was associated with higher all cause mortality (71). Subsequently, a German study concluded that individuals with eGFR < 60ml/min/1.73m^2 had an adjusted risk of cardiovascular death 50% higher than that in those with eGFR above this, but had no increased risk of all cause mortality (68). Further studies of the general population have indicated that renal impairment is independently predictive of MI (74), major adverse cardiovascular events (73) and premature cardiovascular death (75).

Its been reported that CKD stage 3 carries approximately half the cardiovascular risk of that seen with prior MI (72) and that the two together exhibit a composite increased effect on risk; however, other evidence indicates that there does not appear to be a synergistic effect of CKD and cardiovascular disease on outcome (94).

1.6.2 CKD and outcome following MI

It is the post MI studies assessing milder forms of renal impairment and outcome that have been of greatest interest to academia; these are summarised in Table 1.2. These studies are difficult to directly compare as they have varied in a number of different ways: drug study versus registry; type of myocardial infarction and; method of measuring renal function and

defining renal impairment. However, they are largely in agreement that mild to moderate renal impairment is independently associated with adverse outcome.

The degree of increased risk of adverse outcome is somewhat impressive. The earliest study by Wlash et al in 2002 found an adjusted hazard ratio of 2.4 for death for those with abnormal serum creatinine (76); in other early studies, renal impairment carried twice to four times the adjusted risk of death following thrombolysis for acute STEMI (43,79). In the modern era of early or immediate coronary angiography for acute coronary syndromes, there is seen to be an increased adjusted risk of 20% of death for every ten point fall in CrCl (84). Many post MI drug trials generate separate publications assessing renal impairment and this has been done with valsartan (38), captopril (95), clopidogrel (39) and bilvalirudin (83); they all agree that mild renal impairment independently predicts poorer outcome.

1.6.2.1 CKD and outcome with other coronary artery disease

Of course, MI is only one method by which coronary artery disease exerts a clinical effect and renal impairment has been demonstrated to influence outcome in a variety of other disease processes. In chronic stable angina, it as been shown that CrCl independently predicts cardiovascular death or MI (96). Renal impairment has also been demonstrated as a marker of adverse outcome following elective PCI (97-99) with both drug eluting or bare metal stents and the presence and severity of renal impairment pre-CABG correlates well with 5 year outcome (100,101). Even patients with positive nuclear perfusion scanning but angiographically insignificant coronary artery disease do less well if their eGFR is < 60ml/min/1.73m^2(102).

	n	Patient characteristics; mean age (years)	Prevalence of renal impairment	Risk associated with RI
Walsh et al 2002 (76)	483	Acute MI;	22% Cr > 133μmol/l	ACM HR 2.4 abnormal v normal Cr
Muellar et al 2004 (41)	1400	UA/NSTEMI; 65	12.6% eGFR < 60	ACM HR 2.55 eGFR < 60 v > 60
Sorensen et al 2002 (77)	6252	MI		HR ACM 1.4 CrCl 41-55 v CrCl >85
GRACE 2003 (45)	11774	ACS and STEMI; 65.4	35.5% CrCl < 60	ACM RR 2.1 CrCl 30-60 v > 60
Freeman et al 2003 (78)	889	ACS; 63.9	35% CrCl < 60	ACM HR 1.74 per 30 point fall in CrCl
Hobbach et al 2003 (79)	352	Thrombolysed MI; 61.2	24.7 % Cr > 1.2mg/dl	OR ACM 4.8 Cr 1.2-2.8 v Cr <1.2
Gibson et al 2003 (43)	16710	Thrombolysed MI; 61.3	14.5% CrCl < 60	OR death 2.06 CrCl 30-60 v CrCl > 90
SAVE 2004 (40)	2183	Post MI, LVEF< 40%; 59.4	33% eGFR < 60	eGFR < 60 HR 1.30 for ACM v eGFR>60
VALIANT 2004 (38)	14527	Post MI, LVSD/HF; 64.9	33.4% eGFR < 60	HR for ACM 1.10 for 10 point fall eGFR
Masoudi et al 2004 (42)	2706	STEMI/unstable angina	41 % eGFR < 60	HR 2.72 ACM for eGFR 30-60 v eGFR > 90
Schiele et al 2006 (81)	754	STEMI and NSTEMI		1 year mortality 9.4% (eGFR 30-60) v 2.3% (eGFR > 60)
Yan et al 2006 (44)	3510	ACS; 65.4	32% CrCl < 60	ACM HR 1.82 CrCl 30-60 v CrCl> 90
Pitsavos et al 2007 (82)	2172	ACS; 67.2	32.1% CrCl < 60	HR 3.03 ACM for CrCl < 60 v CrCl l> 60
Keltai et al 2007 (39)	12253	ACS without STE; 64.2	26.6% eGFR <60	eGFR < 64 10% mortality v eGFR >81 3.6% mortality
Mehran et al 2009 (83)	13819	ACS/angiography	19.1% CrCl < 60	CKD worse 30 day and 1 year outcome
Seyfarth et al 2009 (84)	4701	pPCI/NSTEMI treated with early PCI		HR 1.21 for ACM per 10 ml fall in CrCl

Table 1.2 Epidemiological studies assessing mild to moderate renal disease and outcome in post MI populations. [RI, renal impairment; ACM, all cause mortality; CVS, cardiovascular; OR, odds ratio; HR, hazard ratio; Cr, creatinine, UA, unstable angina; STEMI, ST-elevation MI; NSTEMI, non ST-elevation MI, ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; pPCI, primary PCI]

1.6.3 CKD and outcome in HF

Arguably, the most extreme form of cardiovascular disease is HF with or without LVSD; morbidity and mortality in these patients is extremely high. As with the general population and post MI cohorts, a number of studies in the past decade have investigated the influence of renal impairment on outcome. This as incorporated sub analysis of drug trials, registry data and observational studies; they are summarised in Table 1.3.

	n	Patient characteristics; mean age (years)	Prevalence of renal impairment	Risk associated with RI
SOLVD 2000 (85)	5684	EF < 35%; 59.2	26% CrCl < 60	ACM RR 1.41 eGFR < 60 v > 60
PRIME-II 2000 (48)	1906	NYHA 3-4 HF, EF < 45%; 64.7	50% eGFR < 58	ACM RR 2.85 eGFR 44-58 v eGFR > 76
Jong et al 2002 (86)	38702	Hospitalised HF; 75.5	-	OR ACM 2.4 for renal disease
Mahon et al 2002 (49)	585	HF, LVEF < 45%; 65.0	50% CrCl < 63.8	ACM OR 0.5 log CrCl
Smilde et al 2004 (87)	161	HF, EF < 45%; 60.0	Mean CrCl 78	CVS RR 1.16 per 10ml drop in CrCl
McAlister et al 2004 (50)	1042	Clinical HF; 67.3	55.5% CrCl < 60	ACM OR 1.70 CrCl 30-60 v > 90
Akhter et al 2004 (88)	481	Hospitalised HF; 62	50% Cr > 1.5mg/dl	OR 2.7 ACM Cr >1.5 v < 1.5mg/dl
Jones et al 2004 (89)	988	HF PEF; 67	Mean eGFR 62	ACM OR 1.5 per 1 SD fall in eGFR
De Silva et al 2005 (47)	1216	Symptomatic HF, EF < 45; 71	57% eGFR < 60	Mortality eGFR 30-60 (36%) v eGFR >90 (18%)
CHARM 2006 (46)	2680	NYHA 2-4 HF; 65	35% eGFR < 60	HR 1.5 ACM eGFR 45-60 v > 60
Khan et al 2006 (90)	6640	LVEF < 35%; 70	33% eGFR < 60	ACM HR 1.3 eGFR 30-59 v > 90
ADHERE 2005 (92)	33040	Acute decompensated HF; 72.4	29% renal insufficiency	Crude mortality BUN > 43 (8.9%) v < 48 (2.7%)
OPTIMIZE HF 2008 (91)	48612	Hospitalised HF; 73.1	19.6 Renal insufficiency	OR ACM 1.48 in admission precipitated by WRF

Table 1.3 Epidemiological studies assessing mild to moderate renal disease and outcome in HF populations. [RI, renal impairment; ACM, all cause mortality; CVS, cardiovascular; OR, odds ratio; HR, hazard ratio; PEF, preserved EF; WRF, worsening renal function]

The overall conclusion is similar in all of the studies, that is, that even mild renal failure is independently predictive of poor outcome. Most of the studies have involved hospitalised HF patients; these patients are generally at the advanced stage of HF and prognosis is generally very poor. Despite this, mild renal impairment has been reported as carrying twice the adjusted risk of death compared to patients with normal renal function (48,86,88), usually using serum creatinine cut-offs or CrCl. More recent studies have used eGFR and CKD guidelines (46,47,90) , but the conclusion is largely the same.

Most of these studies have investigated HF associated with LVSD (47-49,85,87,90) but renal impairment is still predictive of poor outcome in HF associated with preserved ejection fraction(46,89).

1.7 Change in renal function

The vast majority of studies investigating CKD and outcome have assessed renal function at a single time point only. Cardiorenal interaction is a dynamic process and it would seem that analysing change in renal function over time might help in the understanding of cardiorenal disease processes. A number of studies have now been performed tracking change in renal function over time, the majority of which have involved patients hospitalised with HF or MI. Given what has already been discussed, it would be expected that deteriorating renal function would be associated with poorer outcome, and this is indeed what has been found.

The methods of tracking change in renal function over time has varied between different studies; some have monitored change in eGFR but others have defined worsening renal function (WRF) as a change in serum creatinine, using predefined cut-offs. These creatinine cut-offs have also varied between studies, with varying sensitivity and specificity in predicting mortality (103).

The majority of studies assessing changing renal function have addressed populations with established cardiovascular disease, although some studies in the general population have been performed. Recently, it has been identified that rapid decline in renal function (defined as a fall in eGFR of > 3 ml/min/1.73m^2 per year) in the elderly population is independently

associated with HF, MI and peripheral vascular disease (although not with stroke), and this was seen irrespective of baseline renal function (104). Of course, eGFR declines normally with age but 24% of this large cohort exhibited a "rapid" decline in eGFR.

MI itself leads to decline in renal function and this has been demonstrated in both animal models (105) and humans (106,107). A first MI leads to a mean fall in eGFR of 2.2 ml/min/1.73m^2 per year compared to a fall of 0.5ml/min/1.73m^2 per year in controls (106).This is probably largely driven by the renin-angiotensin system, as drug therapy inhibiting this hormonal cascade has been shown to preserve renal function (107,108). WRF is associated with adverse prognosis following MI. Goldberg et al (109) demonstrated that 9.6% of patients with a ST elevation MI had a rise of > 0.5mg/ml whilst in hospital, and these patients had an adjusted HR of 7.22 for death at one year. Sub analysis of the SAVE study (95) in patients with MI and LVSD found that 12.0% had an increase in serum creatinine of >0.3mg/ml in the two weeks after MI, and prognosis was poorer in this group with HR of 1.6 for all cause mortality.

Using change in creatinine also identifies patients at increased risk even with less severe MI. 9% of patients with ACS exhibit a transient or sustained rise in creatinine of >0.5mg/ml while in hospital and these individuals were twice as likely to be dead in 6 months, even if their creatinine improved (110). Using change in eGFR over time also identifies patients at higher risk after MI. In 2009, Mielniczuk et al (111) showed that 5% of patients had a 25% fall in eGFR in the month following ST elevation MI or NSTEMI; these patients subsequently sustained more deaths, further MI, HF and strokes. This decline in renal function and adverse

outcome is associated with systemic inflammation, as evidenced by raised C-reactive protein (CRP).

Tracking change in renal function in patients with HF has also been studied. The majority of studies have concentrated on in-hospital change in renal function, with WRF uniformly associated with poorer outcome. WRF in hospitalised HF is more likely in patients with prior HF, DM, CKD at baseline, use of calcium channel blockers and higher use of loop diuretics (112). The earliest published study in 2000 (113) found that 27.9% of patients over 65 years old admitted to hospital with HF exhibited WRF (>0.3mg/ml change in creatinine); this was associated with longer hospital stays and over twice the risk of in-hospital mortality. A very similar study published in 2004 quoted an adjusted HR for in-hospital death of 7.4 for WRF, using the same criteria (114); another similar study, although smaller, found that WRF was associated with longer hospital stay but had no influence on mortality (115). Akhter et al (88), in 2004, used a more stringent criteria for WRF, namely an increase in creatinine of > 0.5mg/ml in patients with decompensated HF; 36% of study patients fulfilled this criteria, and they had twice the mortality rate at 6 months compared to patients with stable renal function. Patients admitted to hospital with HF and preserved LV ejection fraction have also been studied (116); 12% exhibited a 25% fall in eGFR during their in-patient stay. This was associated with an adjusted HR of 2.0 for all cause mortality and 2.5 for cardiovascular death after 7 years, but only in those with CKD stage 3 or worse at baseline.

Some work has been done on tracking renal function after hospital admission in HF. Damman et al followed up 1023 patients admitted with HF for 12 months (117). 11% had a rise in creatinine >0.3mg/ml whilst in hospital with 16% exhibiting this at 6 months and a further

9% at 12 months. WRF at any time was associated with twice the risk of death or readmission with HF. Khan et al (90) tracked eGFR in patients with HF and LVSD over 3 years as part of the SOLVD study. A rapid decline in eGFR of >15 ml/min/1.73m^2 per year had an adjusted HR of 5.6 for all cause mortality, compared to those with a fall in eGFR of < 5ml/min/1.73m^2.

1.8 Mechanisms of cardiorenal interaction

As demonstrated, CKD is common in cardiovascular disease states and impairs prognosis, whilst cardiovascular disease leads to progressive renal damage. This adverse cardiorenal interaction is driven by traditional and non-traditional cardiovascular risk factors, as well as the RAAS. These are discussed in detail below.

1.8.1 Traditional risk factors

As demonstrated below, traditional cardiovascular risk factors are more prevalent in patients with impaired renal function. Indeed, renal insufficiency may be a simple surrogate marker of the duration or severity of these risk factors.

1.8.1.1 Hypertension

Hypertension is very prevalent in developed countries, but is certainly found at higher rates in those with CKD. Studies have found 20 to 50% of the general population have evidence of hypertension; these same studies have demonstrated a two to three-fold higher rate of hypertension in those with even mild CKD (67,71,93,118). In cohorts of patients with MI, the prevalence of hypertension is 40 to 60%, being 30-50% more common on those with CKD

(38,39,45,80). In HF cohorts, hypertension is 20% more common in CKD than those with normal renal function (47,85).

1.8.1.2 Diabetes Mellitus

DM is found in 5 to 10% of the general population, but the rate in those with CKD is double that (67,68,71,118). In MI cohorts, the prevalence of DM is consistently around 20%, with CKD patients having a rate 25-50% higher (38,39,45,80).

1.8.1.3 Dyslipidaemia

Dyslipidaemia is 20-50% more common in CKD (68,71,93) compared to the general population. The entire lipid profile is generally worse in CKD, with high LDL, high triglycerides and low HDL (118).

1.8.1.4 LV hypertrophy

LV hypertrophy is widely recognised as a strong predictor of adverse cardiovascular outcome and this is approximately twice as common in CKD as in those with normal renal function (67,119).

1.8.1.5 Elevated BMI

Obesity is a soft cardiovascular risk factor, but some studies have shown CKD to be associated with a higher mean BMI (68,118). However, recent evidence indicated that elevated BMI is not independently predictive of adverse outcome in CKD (120).

1.8.1.6 Age

As renal function deteriorates with increasing age, it is thus to be expected that CKD is much more common in the elderly population. Increased age is one of the strongest predictors of cardiovascular disease; indeed age is one of the strongest confounding issues that need to be addressed when assessing kidney disease and cardiovascular outcomes. Those with an eGFR of 45-60ml/min/1.73m^2 can be expected to be anything from two to seven years older than those with an eGFR of > 60ml/min/1.73m^2 (38,46,68,71,80).

1.8.1.7 Smoking

The studies disagree with regard to the rate of smoking in CKD, compared to those with normal renal function. Some indicate that renal impairment is associated with a 50 to 200% higher rate of smoking (67,93), although other studies have smoking rates in CKD one quarter to one half that of the general population (45-47,68,80,118). This latter finding could be explained by smokers living less long, and thus less likely to be included in usually older cohorts of CKD. However, some of these studies indicate that current smoking is higher with normal renal function, although total pack years, rates of "ever smoked" and history of smoking do not differ between renal function class (47,80,118); this might suggest that the development of kidney disease promotes smoking cessation!

1.8.1.8 Gender

Male gender carries less favourable prognosis, particularly with regard to cardiovascular disease. However, given that females have a lower mean eGFR, it's therefore not surprising to find that females make up a relatively higher proportion of patients with CKD and this is reproduced in the general population, MI cohorts and HF cohorts(38,67,71,73,80,85,93).

Thus, male gender would be the only traditional risk factor for cardiovascular disease that is less prevalent in CKD.

1.8.2 Non-traditional risk factors

As discussed, there is a higher rate of traditional cardiovascular risk factors in those with CKD, but this is not thought to completely explain the higher rate of cardiovascular disease. Thus, the phenomenon of non-traditional risk factors has become increasingly recognised (121). The more important examples of these are discussed below, but other examples include anaemia, oxidative stress, electrolyte and fluid imbalance and thrombogenic factors (121); these are all more prevalent in kidney disease and will theoretically promote cardiovascular pathology.

1.8.2.1 Coronary artery calcification

Deposits of calcium appear and accumulate in coronary atheroma, particularly when it has been present for a considerable period of time. This coronary artery calcification is much more common in patients with kidney disease than in the general population (122); it is almost universal in patients with ESRF (123) and has been reported in two thirds of patients with CKD stage 3 or worse (124). As well as being more common in renal failure, coronary artery calcification also progresses much quicker in these patients (123-125).

Coronary artery calcification occurs in the intimal plaque in both renal and non-renal patients. However, calcification within the media appears to occur only in patients with renal impairment (126); this pattern of calcification has been termed Monckeberg's sclerosis and is demonstrated to be a manifestation of accelerated atherosclerosis (127).

This adverse calcification in CKD is secondary to abnormal regulation of calcium and phosphate related to disturbances in vitamin D and parathyroid hormone concentrations. Coronary artery calcification mirrors bone mineralization, and becomes increasingly prevalent as renal impairment, and thus calcium homeostasis, deteriorates. In addition to the more apparent harmful consequences of coronary artery calcification (angina, MI, LVSD), calcification of the arterial tree contributes to arterial stiffness, hypertension and left ventricular hypertrophy, all of which are associated with cardiovascular mortality.

1.8.2.2 Hyperhomocystinaemia

Elevated serum levels of homocysteine are thought to increase the risk of cardiovascular events. This has been demonstrated in patients with coronary artery disease (128) and DM (129); studies in the general population have revealed conflicting results as to whether hyperhomocystinaemia correlates with cardiovascular morbidity (130,131).

Serum homocysteine levels are certainly elevated in patients with renal impairment compared to those with normal renal function; eGFR is inversely proportional to homocysteine levels (132) with patients with eGFR < 60 ml/min/1.73m^2 having a mean serum level 50 to 60% higher than those with an eGFR > 90 ml/min/1.73m^2 (133). However, hyperhomocystinaemia has not been shown to independently predict cardiovascular outcome in patients with CKD stage 3 or 4 (132). It may be that renal impairment may be the confounding factor that explains the association between homocysteine and mortality.

1.8.2.3 Inflammation

Atherosclerosis is now considered an inflammatory disease (134) and there is certainly convincing evidence to show that systemic inflammation, usually measured as CRP, is associated with adverse cardiovascular outcomes (135-137). Renal failure itself is associated with inflammation. In ESRF, CRP levels are particularly high and strongly predict adverse cardiovascular outcome (138,139). This association also extends to less severe forms of renal impairment where CRP is shown be elevated in patients with CKD stage 3 and 4 and independently predicts cardiovascular mortality (133,140-142). Elevated fibrinogen is another marker of inflammation; this is also seen to be elevated in milder forms of renal failure and again predicts adverse cardiovascular outcome (142).

Indeed, elevated CRP is also associated with progression of CKD in the general population (143) and following MI (111); it may be that systemic inflammation in the over-riding link between renal and cardiac disease.

1.8.2.4 Proteinuria

Urinary protein is an abnormal finding and in the absence of fever or urinary infection is indicative of renal dysfunction. Proteinuria is much more common in diabetic patients, where it is seen in over one third (144), but is also seen in non-diabetic, usually hypertensive patients (145,146). Even in the absence of hypertension or DM, 6% of the population will exhibit proteinuria (147). Proteinuria, even at very low levels (microalbuminuria) is a strong independent predictor of cardiovascular disease and this has been demonstrated in wide variety of populations (144,146-151)

In both diabetic and non-diabetic patients, those with proteinuria have higher prevalence of traditional cardiovascular risk factors such as hypertension, dyslipidaemia and smoking (146,147,149) but these do not fully explain the higher cardiovascular morbidity and mortality. Proteinuria may be a marker of systemic inflammation (143,152), more severe end-organ damage, endothelial dysfunction or abnormalities in coagulation or fibrinolytic systems (57), all of which will promote adverse cardiovascular events.

1.8.3 The renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) undoubtedly plays a large role in both cardiovascular disease and renal disease and is thus probably a key cog in cardiorenal interaction. This hormonal cascade starts with renin, secreted from the kidney in response to reduced renal perfusion; this stimulates the conversion of hepatic derived angiotensinogen to angiotensin I, an inactive decapeptide. This in turn is converted to angiotensin II by angiotensin-converting enzyme (ACE) which is found in the pulmonary vasculature. Angiotensin II has a variety of different effects on vasculature, cardiac function and renal action. It also stimulates aldosterone production from the adrenal glands. The overall net effect of this is an increase in systemic blood pressure, salt and water retention and increased cardiac output. The RAAS thus plays an important role in fluid and haemodynamic homeostasis; however prolonged or inappropriate activation of the RAAS ultimately leads to progressive deterioration in cardiac and renal function, as demonstrated in Fig 1.1. MI, LVSD and HF are all associated with increased RAAS activity.

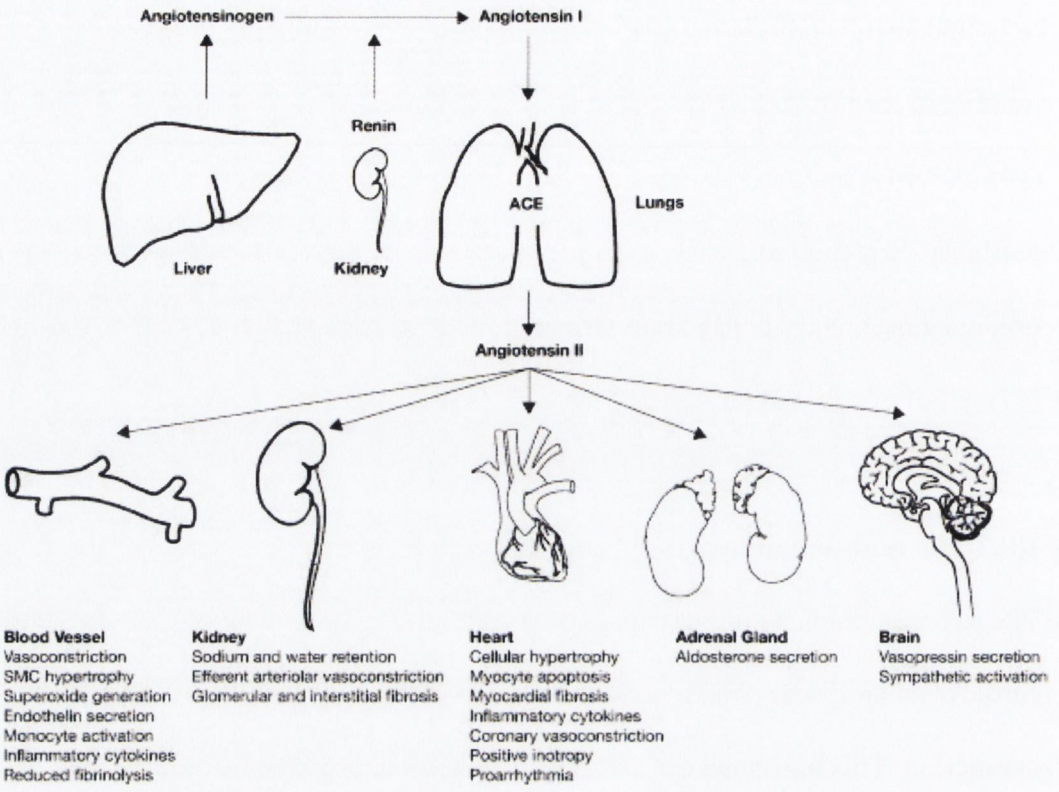


Figure 1.1 The renin-angiotensin-aldosterone system and its adverse effects

Angiotensin II has a number of adverse cardiac effects. Vasoconstriction and salt and water retention leads to increased LV wall stress, thus promoting LVH. It also has a direct toxic effect on myocytes leading to myocyte apoptosis and ultimately fibrosis (153). Aldosterone itself has numerous adverse effects on the cardiovascular system, including promotion of myocardial fibrosis, stimulation of myocyte apoptosis, increase in sympathetic drive, and potentiation of fluid overload and electrolyte imbalance (154,155). The RAAS has an equally adverse effect on renal function. Angiotensin II, in addition to causing systemic hypertension, alters the vascular tone of both efferent and afferent arterioles. This leads to increased glomerular pressure causing mechanical stress to podocytes and destruction of the glomerular basement membrane. This ultimately leads to progressive atrophy, cell death and subsequent fibrosis resulting in irreversible loss of nephron function (156). This is further compounded

by the action of aldosterone which accelerates renal decline by sustaining cell hypertrophy, inflammation and fibrosis (157).

1.8.3.1 Pharmacological blockade of the RAAS

Given the undoubted harm caused by RAAS stimulation, a number of pharmacological therapies have been developed which act to inhibit its action. These drugs interrupt at different stages along the pathway and evidence indicates that this leads to improved clinical outcomes. ACE-inhibitors act to prevent the production of angiotensin II, whilst angiotensin receptor blockers (ARB) compete with angiotensin II, thereby reducing its effect. Aldosterone receptor antagonists such as spironolactone and eplerenone have been developed. Furthermore, renin inhibition is now the new front on tackling the RAAS, in the form of aliskiren.

Inhibition of the RAAS has undoubted benefits in HF and following MI; ACE-inhibitors such as enalapril (158), ramipril (159) and captopril (160) reduce mortality and improve symptoms, as do ARBs in the form of candesartan (161) and valsartan (160). Spironolactone and eplerenone improve prognosis in NYHA class III HF and post MI respectively (162,163). ACE-inhibitors may also act to reduce the progression of atherosclerosis, as evidenced by reduced MACE with ramipril (164) and perindopril (165) in patients without MF or MI. There is also experimental evidence that aliskiren prevents atherosclerosis progression.(166)

RAAS inhibition also protects renal function. In addition to preventing MACE, ramipril use in diabetics reduced the progression to overt nephropathy by 25% (150) and captopril preserves renal function after MI (107). Indeed the evidence of benefit of ACE-inhibitors and ARBs in CKD is such that these therapies provide the mainstay of managing both diabetic

and non-diabetic CKD, irrespective if hypertension is present or not (25). An outstanding argument is whether combination therapy with ARB and ACE-I is synergistic (156,167). Its worth noting that the introduction of an ARB or ACE-I may cause a transient fall in eGFR but this should be tolerated in if it is less than 25% from baseline (25).

Aldosterone blockade has as yet no role in CKD management but there are arguments for trialing its use (168,169) whilst aliskiren has been shown to add nephroprotection when used in conjunction with losartan in diabetic nephropathy (170).

1.9 Treatment of cardiac/renal disease; effect on the other system

It is therefore well demonstrated that cardiac and renal function are closely intertwined. This would lead to the question; does beneficial treatment on one system lead to benefits on the other? There certainly does appear to be evidence to suggest that this is the case. Renal transplantation is associated with lower cardiovascular morbidity and mortality compared to patients who remain on the transplant waiting list (171). In patients with LVSD and end stage renal failure, the receipt of a renal transplant leads to a dramatic increase in LV ejection fraction after 12 months, as well as improvement in NYHA functional class (172).

Renal transplantation has also been reported to lead to echocardiographic regression of left ventricular hypertrophy (173); however, echocardiography overestimates left ventricular mass in haemodialysis patients (174) and a recent cardiac MRI study has concluded that renal transplantation has no measurable effect on LV mass (175).

Cardiac transplantation does not lead to improvement in renal function; however, this is largely due to the necessary use of nephrotoxic calcineurin inhibitors to prevent rejection. However, in chronic HF, both cardiac resynchronisation therapy (176) and left ventricular assist devices (177) have been shown to improve renal function. ACE-inhibitors have been shown to reduce mortality following MI (107,108) but also prevent decline in renal function.

1.10 Cardiorenal Syndromes

Given the increasing complexity of cardiorenal interaction, recent efforts have been made to classify particular disease processes where cardiac disease and renal disease influence the other. This has lead to the idea of cardiorenal syndromes, of which five have been identified (178):

1. Cardiorenal syndrome type 1 (acute cardiorenal syndrome): This is characterised by acute kidney injury which is directly due to a rapid worsening of cardiac function. This may be seen following acute MI or acute heart failure.
2. Cardiorenal syndrome type 2 (chronic cardiorenal syndrome): This is characterised by long standing cardiac disease, such as chronic heart failure, leading to progressive deterioration in renal function.
3. Cardiorenal syndrome type 3 (acute renocardiac syndrome): Acute renal failure of any cause leads to acute cardiac dysfunction; this could be arrhythmia due to electrolyte disturbance of acute left ventricular failure secondary to salt and water overload.
4. Cardiorenal syndrome type 4 (chronic renocardiac syndrome): Chronic renal disease leads to increased cardiac disease, as manifest by left ventricular hypertrophy, diastolic dysfunction or increased rate of adverse cardiovascular events

5. Cardiorenal syndrome type 5 (secondary cardiorenal syndrome): Both renal and cardiac dysfunction result from a separate disorder, for example, amyloidosis, vasculitis etc

This classification system certainly helps to clarify the different clinical situations where the heart and kidney are both diseased. Cardiorenal types 2 and 4 are probably the scenarios which are more relevant when we examine epidemiology of renal dysfunction, cardiovascular disease and long term outcome.

It is important to recognise how this system could have a role in clinical care of patients, and accept that the label of "cardiorenal syndrome" is less important than the understanding the adverse process. For example, if we take a patient with hyperkalaemia and acute renal failure who suffers a ventricular arrhythmia and pulmonary oedema, documenting this scenario as "cardiorenal syndrome type 3" would do little to simplify patient management. Rather, as the creators of this classification system attest, an appreciation of the pathophysiology should lead a physician to primarily concentrate on correcting renal function rather than initiating cardiac based therapies.

1.11 Natriuretic peptides, cardiovascular disease and CKD

Over the past decade, the natriuretic peptides have stimulated much interest in cardiovascular and renal academia. Atrial natriuretic peptide (ANP) was the first such peptide to be discovered (179) over 25 years ago, followed soon after by b-type natriuretic peptide (BNP) (180), and subsequently c-type natriuretic peptide (CNP) (181).

BNP, sometimes also called brain natriuretic peptide after it was discovered in porcine brain, has now become the most widely studied natriuretic peptide; a MEDLINE search using "brain natriuretic peptide" as a keyword generates 6203 publications. BNP is produced predominately in the ventricular myocytes and secreted from the heart via the coronary sinus (182). BNP consists of 32 amino acids and is produced by cleavage of proBNP into BNP and the biologically inactive N-terminal BNP (NT-BNP).

The main stimulus for BNP secretion is ventricular stretch due to volume or pressure overload (183). As such, serum levels of both BNP and NT-BNP have now been extensively studied as potential diagnostic and prognostic markers of a variety of cardiovascular disease states such as hypertension, LVSD, HF and others.

1.11.1Physiological effect of BNP

BNP's primary role is to act as a compensatory mechanism in cardiovascular disease states to reduce cardiac preload; it does this via direct actions on the vasculature and kidneys. BNP causes relaxation of human arteries, thus leading to systemic vasodilatation and a fall in blood pressure (184). It also promotes both natriuresis and diuresis (185,186) by increasing the eGFR and ultrafiltration coefficient due to mesangial cell relaxation, inhibition of proximal tubule solute transport and reduction in sodium resorption in the collecting tubules (187,188). Furthermore, natriuretic peptides also appear to counteract both RAAS and sympathetic activity (187,188).

All of these effects are evidently beneficial, particularly for a heart that is under increased strain. However, it appears that BNP effects of vasodilatation and natriuresis are blunted in

patients with heart failure (189-191); this has lead to the development of synthetic BNP (nesiritide), administration of which may be beneficial in decompensated HF patients(192,193).

1.11.2 Serum measurement of BNP

Normal human serum concentrations of BNP ranges from 4 to 35 pg/ml and there has been much research into how interpretation of elevated BNP levels can help in diagnosis and predicting prognosis in cardiovascular disease. A number of non-cardiovascular factors can influence BNP concentrations and can thus influence interpretation; BNP is higher in females and also increase with age (194,195). Body weight has an inverse relationship with BNP, and changes in BMI can influence serum BNP levels (196,197); this may be explained by the abundance of natriuretic peptide clearance receptors found in adipose tissue (198). Anaemia is also associated with higher natriuretic peptide levels (199-201).

Cardiovascular disease is certainly associated with raised natriuretic peptides. BNP levels are raised in hypertension, LVH (202,203), following MI and in HF and LVSD (204-206). Elevated BNP following MI is strongly predictive of outcome (204-207), independent of ECHO findings (208); high BNP predicts death, re-infarction, adverse cardiac remodelling and development of HF.

Most academic interest has been concentrated on BNP in HF and LVSD; levels are certainly raised in these conditions, although probably correlate better with NYHA classification rather than left ventricular function (209). As such, the possibility of using BNP as a mass screening tool to identify these disorders in the community has been postulated. Initial results seemed

promising at identifying asymptomatic LVSD and high risk patients from the general population (210,211) or even as a "rule-out" test for general practitioners concerned about HF (212). However, analysis of Framingham data (213) was less impressive and recent evidence suggest that BNP is not accurate in low risk groups, possibly because of the influence of age and gender (214,215).

The use of BNP or NT-BNP as a diagnostic tool in patients presenting to hospital acutely with breathlessness has also been studied. They improve the diagnosis rate of acute HF over clinical judgement alone (216,217) and also add prognostic information on these patients (218). Another possible use of BNP is to direct and monitor the out patient treatment of chronic HF (219,220).

1.11.3 Natriuretic peptides and renal disease

Renal disease has proven to be a significant confounding issue with BNP and cardiovascular disease. BNP and NT-BNP are both excreted from the kidneys (221). As such, renal impairment is associated with higher serum natriuretic peptide levels and an inverse relationship exists between eGFR and BNP. In hypertensive patients, those with serum creatinine >1.6mg/dl have significantly higher BNP than those with BNP below this level (222); patients on haemodialysis have grossly elevated BNP levels (223) but levels do fall after dialysis and natriuretic peptides have been identified in dialyslate (224).

The influence of renal failure on BNP levels is still influential even in situations where BNP is very elevated. Luchner et al (225) demonstrated that in patients who had sustained a MI, the presence of renal impairment was associated with twice the concentration on BNP (132 v

68pg/ml). Furthermore, BNP levels did not differ between patients with LVSD and normal renal function and patients normal LV function and renal impairment; this suggests that renal impairment influences BNP levels to the same degree as LVSD.

In addition to reduced renal excretion of BNP, renal impairment will be associated with higher rates of hypertension, LVH, LVSD and increased fluid, all of which will further increase mean BNP levels. This has led to widespread discussion as to whether natriuretic peptides will be less accurate, or even inaccurate, at identifying cardiovascular disease in patients with CKD (226-229), although increasing the diagnostic cut-off might help in these cohorts. Certainly in the acute setting, increasing BNP cut-offs improved the diagnosis of acute HF in patients with renal disease (228).

1.12 Clinical Research Initiative

The Clinical Research Initiative (CRI) was set up in the Western Infirmary, Glasgow in the early 1990's under the supervision of Professor Henry Dargie, and was initially funded by the Medical Research Council. The CRI was designed as a centre which would allow a wide variety of research to be undertaken, with particular interest in cardiovascular disease and heart failure. Since its inception, it has consistently produced high quality research, generating a large volume of original papers, and continues to do so now almost twenty years later. Its scope incorporates epidemiology, clinical drug trials, cardiac MRI, cardiorenal disease, natriuretic peptides and echocardiography.

One of its original main roles was to act as the centre for the third Glasgow MONICA coronary risk factor survey in 1992. The MONICA (monitoring of trends and determinants in

cardiovascular disease) study has been undertaken in a number of different countries throughout the world, generating valuable epidemiological data regarding cardiovascular disease.

Subsequent to the MONICA study, further similar epidemiological studies were performed in the CRI; these include the ELDERLY cohort study in 1995, the POST-MI study in 1995 and the GP-HF study in 1998. The MONICA, ELDERLY and POST-MI cohorts all underwent further rescreening visits a number of years later and further to this, all four cohorts were again rescreened twice, under the umbrella name of the LIVING study. The main interest of the CRI project in Glasgow was the epidemiology of left ventricular dysfunction and heart failure. The characteristics of each cohort can be summarised thus:

- MONICA cohort – general population in Glasgow.
- ELDERLY cohort – general population in Glasgow aged greater than 55years.
- POST MI cohort – patients in Glasgow area with documented index myocardial infarction in preceeding 2.5 to 11 years
- GP-HF- patients identified from primary care who were prescribed a medication suggesting a diagnosis of heart failure (ACE-Inhibitor, digoxin, loop diuretic)

Figure 1.2 details the chronology of these cohort studies; it is these studies which have generated the data which forms the basis of this thesis.

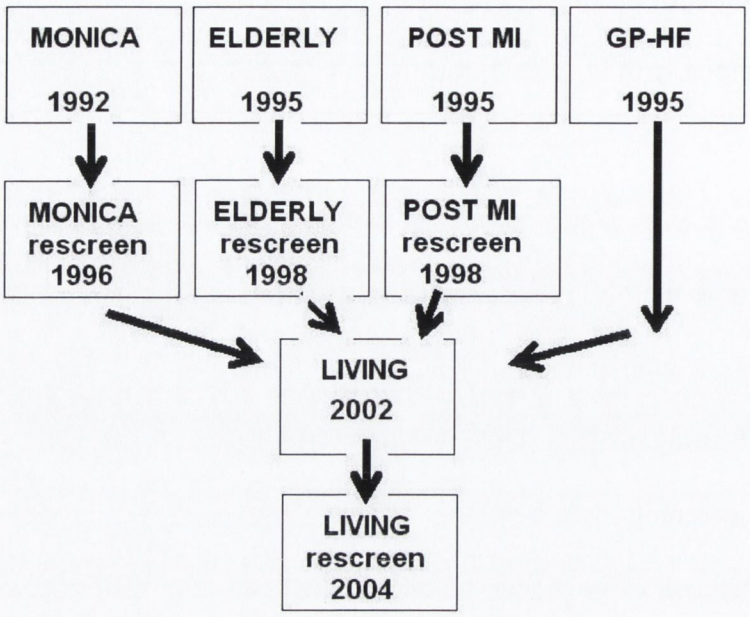


Figure 1.2: Flowchart of major epidemiological screening studies performed in the Clinical Research Initiative, Western Infirmary, Glasgow

Analysis of the 1992 MONICA cohort generated a number of published papers. These looked at: the prevalence of symptomatic and asymptomatic LVSD(4); the use of brain-natriuretic peptide at identifying LVSD in the community(210,211) and; the prevalence of positive Helicobacter pylori serology in the community, and its association with coronary heart disease (230).Analysis of the MONICA data also served as the basis of an MD for Dr Theresa McDonagh, awarded by the University of Glasgow.

The 1995 ELDERLY cohort study served as the basis of a MD for Dr Stephen Robb, awarded by the University of Glasgow. Analysis of he POST-MI cohort study of 1995 produced one paper, which assessed the prevalence of haemochromatosis gene mutation and its association with ischaemic heart disease (231). Two papers have been produced from analysis of the GP-HF cohort study from 1998 (232,233) which assessed patient differences in management of

heart failure in primary care and hospital, and the ability of BNP to identify HF in the community.

In the analysis of the CRI cohorts performed thus far, renal function has never been assessed. Additionally, long term mortality outcome in these cohorts has not been fully addressed: only three year outcome for the GP-HF cohort (233) and four year outcome for MONICA have been analysed (210).

1.13 Conclusion

Cardiovascular disease causes significant morbidity and mortality within developed countries. Chronic kidney disease, even when mild, carries an increased risk of cardiovascular events and seems to act an independent predictor of adverse outcome in a variety of different populations. Cardiorenal interaction plays an increasingly recognised role in the pathophysiology of both cardiac and renal disease, and understanding of this process may help in future development of treatment strategies.

Within the United Kingdom, Scotland carries the most unfavorable cardiovascular statistics. Glasgow is the largest city in Scotland, and large screening studies of different cohort of Glaswegians have been performed in the CRI, Glasgow within the last two decades, primarily interested in cardiovascular disease.

1.13.1 Hypothesis

My hypothesis is that mild renal failure is common in the Glasgow population, both in the general population and in those with established cardiovascular disease, and that poorer renal function is independently predictive of adverse outcome in these populations.

1.13.2 Aims

This thesis specifically aims to perform novel investigation of the Glasgow CRI cohorts with a particular interest in;

- identifying the range of renal function and prevalence of renal impairment
- identifying predictors of poor renal function
- quantifying the prevalence and influence of other variables and their association with renal function
- quantifying the influence of renal disease on outcome, specifically all cause mortality and cardiovascular death
- assessing change in renal function over time and its association with outcome
- examining the diagnostic and prognostic strength of natriuretic peptides and
- investigating the relationship (if any) between natriuretic peptides and renal function

CHAPTER 2

POST MYOCARDIAL INFARCTION COHORT

2.1 Introduction

Chronic renal impairment is more prevalent in patients who have sustained an MI compared to the general population; recent studies have shown that approximately one third of patients who suffer a MI will have an eGFR of less than 60ml/min/1.73m^2 (38,42,80). Increased age can explain some of this association, as it is an independent risk factor for both cardiovascular disease and CKD. However, conventional risk factors for cardiovascular disease such as DM and hypertension are also the leading aetiologies of CKD (27) and one can argue that CKD and cardiovascular events are simply different adverse outcomes of the same chronic disorders. Furthermore, smoking, obesity and dyslipidaemia are also independent predictors of the development of CKD (53) and it is likely that atherosclerosis is becoming increasingly culpable for CKD, particularly in elderly patients (27).

Not only are patients with CKD more likely to suffer an MI, they carry a less favourable subsequent prognosis that patients with normal renal function (38,42-45,78-81)); for example, adjusted HR for all cause mortality following MI is 1.3 for patients with eGFR less than 60ml/min/1.73m^2 compared to those with eGFR greater than this (80), and 2.72 when compared to patients with eGFR over 90ml/min/1.73m^2 (42).

MI is not the only manifestation of coronary artery disease that an adverse influence of renal impairment is seen. CKD independently predicts poor outcome in chronic stable angina and following CABG or PCI (96-101). Even patients with angiographically insignificant coronary artery disease do less well if their eGFR is less than 60/ml/min/1.73m^2 (102).

Traditional RF can explain some of this adverse prognosis. However, the influence of non-traditional risk factors for cardiovascular disease in CKD are becoming increasingly recognised(57); these include coronary artery calcification (123,124,127), hyperhomocystinaemia (128,132,133), inflammation (133,138,139,142,143) and proteinuria (146,149,150).

Scotland has the worst cardiovascular profile in all of the United Kingdom (1). In this chapter, a cohort of Glaswegians who have sustained a MI will be examined. The prevalence of kidney disease and its influence on long term outcome will be assessed and forms the main focus of this section. This cohort has never been thoroughly studied and LV function, cardiovascular risk profile and symptoms shall also be gauged. Furthermore, the diagnostic and prognostic strengths of natriuretic peptides shall be examined, as will its association with renal function.

2.2 Methods

2.2.1 Subject identification

Subjects who had sustained a first validated MI in the preceeding 2 to 11 years were identified from the MONICA register. The MONICA project maintains a database of all coronary events in selected populations. The Glasgow MONICA project identifies all people resident in North Glasgow aged between 25 and 64 years at the time of MI on the basis of hospital discharge coding, death certificate data from the Registrar General for Scotland, and postmortem and general practitioner data (9).

Two thousand, two hundred and fifty eight people were initially identified from the register as having survived a first MI between 1985 and 1992. As detailed elsewhere (231), from this cohort, nine hundred and twenty four patients attended the CRI, Glasgow for a screening visit in 1995. Subjects had suffered their index MI a median period of 7.0 years (range 2.5–11.5 years) prior to the screening visit.

2.2.2 Screening visit

The screening visit consisted of the following:

Questionnaire

Each participant completed a Personal Health Record questionnaire. This incorporated questions on demography, current medication, medical history including angina, hypertension and DM and answered the Medical Research Council questionnaire on breathlessness (234).

Echocardiography

Standard two-dimensional echocardiography was carried out with the participant reclining at 40°, in the left lateral position. Images were stored on video-tape and analysed online. Echocardiograms were deemed suitable for analysis if greater than 85% of the endocardium was visible. A biplane disc summation method (Simpson's rule) (235) was used to calculate LVEF, the final result being a mean of three cardiac cycles.

Blood pressure

Blood pressure was measured with the participant in a seated position, following 5 minutes of rest, on the right arm using a standard random zero sphygmomanometer. A mean of two readings was used.

Blood sampling

Blood samples were taken from the antecubital fossa. Analysis for blood glucose was performed. BNP levels were measured using Shionoria solid phase immunoradiometric assay from Schering CIS (France). NT –ANP was assesses with a radioimmunoassay from Biotop (Oulu, Finland).

Serum samples were frozen at time of screening. They were subsequently thawed in October 2006 and immediately analysed for creatinine concentration on an Abbott c8000 analyzer using a reaction rate Jaffe method (Abbott Diagnostics, US). Serum creatinine levels have been shown to remain stable when samples are stored at very low temperatures for many years (245). Estimated glomerular filtration rate (eGFR) was then calculated for each individual using the Modified Diet in Renal Disease formula [186 x [Serum Creatinine (μmol/L) x 0.0113]$^{-1.154}$ x Age (years)$^{-0.203}$ (x 0.742 if female)].

2.2.3 Definitions

The definitions used in this study were as follows:

Hypertension was defined as; a history of high blood pressure; a measured blood pressure of more than 140mmHG systolic, more than 90mmHG diastolic, or both; current treatment with anti-hypertensives or; a combination of these factors.

Diabetes mellitus was defined as: a history of diabetes; current treatment with oral hypoglycaemic agents and/or insulin; a blood glucose level greater than 11.0 mg/dL or; a combination of these factors.

Left ventricular systolic dysfunction (LVSD) was defined as a left ventricular ejection fraction of 35% or less.

Symptomatic patients were those who reported angina and/or breathlessness.

Renal impairment was defined using both eGFR and serum creatinine. With eGFR, current guidelines regarding CKD classification were used(24); For CKD stage 1 and 2, guidelines indicate that there must be evidence of kidney damage in the form of proteinuria or haematuria; urinalysis was not available to us and thus we classified patients as CKD stage 1 or 2 based solely on their calculated eGFR. All patients with eGFR < 60ml/min/1.73m^2 were classified as CKD stage 3 or worse (CKD 3+), even if they fulfilled criteria for CKD stage 4 or 5. All individuals with eGFR >90ml/min/1.73m^2 were classified as CKD stage 1 or better (CKD 1-). Renal impairment as defined by serum creatinine utilised previously published definitions used in MI studies(43,79); creatinine between 106 and 177 μmol/l was the criteria for mildly raised creatinine and >177μmol/l classified as markedly raised creatinine. Due to the relatively small number of individuals with creatinine >177μmol/l, all patients with a serum creatinine >106μmol/l were classified as having renal impairment.

2.2.4 Deaths

All deaths up to an including 31st December 2006 were collated from the Scottish Registry office. From the information on death certificates, two experienced cardiologists (Professor Henry Dargie, Dr Therese Mc Donagh) coded the deaths as cardiovascular, cancer, respiratory or other. The cardiovascular deaths were further sub classified as being due to MI, HF, cerebrovascular disease or other. Where information on death certificates was missing or incomplete, the death was labelled as "uncoded".

2.2.5 Statistical analysis

The majority of continuous values were normally distributed and means were compared using an unpaired t-test or ANOVA as appropriate. The exceptions were serum creatinine, NT-ANP and BNP levels, which were compared between groups using a Mann-Whitney test or logarithmically transformed as necessary. Categorical variables were compared using χ^2 test. Correlation between continuous variables was assessed using Pearson's technique. ROC analysis was used to assess the ability of natriuretic peptides to identify LVSD within the cohort, and the ability of serum creatinine to correctly identify individuals with stage 3 CKD or worse.

Kaplan-Meyer analysis was used to compare survival and cardiovascular deaths between groups, with subsequent log-rank testing. Survival between groups was then assessed using Cox regression, and hazard ratios (HR) were calculated. Univariate analysis was performed initially, followed by multivariate analysis; variables that were significantly associated with mortality from the univariate analyses ($p < 0.10$) were included in multivariate models. The specific variables included in the multivariate analysis are highlighted in the results section: briefly, age, LVEF, DM, hypertension, ACE-inhibitor therapy, beta-blocker therapy, statin therapy and breathlessness were used for all cause mortality; the same variables were used for cardiovascular deaths with the exception of statin therapy. The same models were used for subsequent analysis of BNP and renal function.

All analysis was performed using SPSS or Minitab. A p value of less than 0.05 was considered statistically significant.

2.3 Results

2.3.1Patient demographics

2.3.1.1 Baseline characteristics

Nine hundred and twenty four individuals completed the screening process. Baseline characteristics of these individuals are summarised in Table 2.1. The majority of the cohort were male (73.2%) with a mean age of 61.3 ± 7.3 years at the time of screening. Age ranged from 34.7 to 75.4 years old (Figure 2.1), with the majority of individuals (62%) older than 60 years. The average age at time of index MI was 54.5 ± 7.1years, with screening taking place a mean of 6.9 ± 2.4 years later.

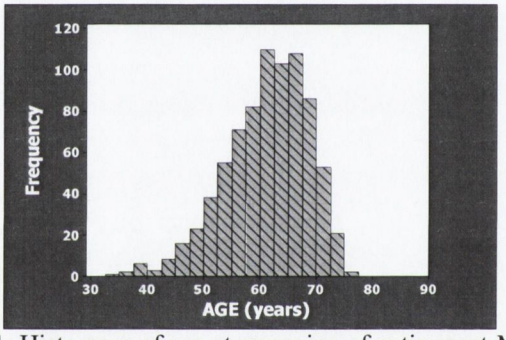


Figure 2.1: Histogram of age at screening of entire post-MI cohort

Almost two thirds fulfilled the criteria for hypertension (64.5%) and DM was seen in one tenth of the cohort (10.8%). Reported symptoms were very common, with only 18.8% denying breathlessness or angina. Angina was reported by 69.7% and breathlessness by 60.9%.

Medications were widely prescribed in the cohort, although 8.8% were not taking any prescribed medications at all. The mean number of medications per subject was 2.4, although some individuals were taking as many as seven. Aspirin (76.3%) and nitrates (51.4%) were by far the most commonly prescribed drugs. The rate of ACE-inhibitor, beta-blocker and statin use was modest, at 16.8%, 30.3% and 7.6% respectively

	Baseline characteristics	
		range
n	924	-
Age (years)	61.3 ± 7.3	34.7 - 75.4
male	677 (73.2%)	-
Age at MI (years)	54.5 ± 7.1	26.6 – 69.0
Time from MI (years)	6.9 ± 2.4	2.5 -11.5
BMI	27.5 ± 4.5	16.5 - 48.0
Height (cm)	165.3 ± 8.9	137.0 -188.0
Weight (kg)	75.3 ± 14.8	36.1 - 128.5
Systolic BP (mmHG)	139.9 ± 23.4	75 - 219
Diastolic BP (mmHG)	80.1 ± 13.0	40 -130
Pulse pressure (mmHG)	59.6 ± 18.6	14-121
Hypertension	596 (64.5%)	-
Diabetes Mellitus	100 (10.8%)	-
Glucose (mmol/l)	5.35 ± 2.3	1.8 - 22
LVSD	146 (15.8%)	-
LVEF (%)	46.7 ± 12.4	11-76
LVDD (cm)	5.4 ± 0.8	3.6 – 9.0
Angina	644 (69.7%)	-
SOB	563 (60.9%)	-
Symptomatic	750 (81.2%)	-
Medication		
Number of medications	2.6 ± 1.4	0-7
No medications	81 (8.8%)	-
Thiazide	69 (7.5%)	-
Loop diuretic	186 (20.1%)	-
Aspirin	705 (76.3%)	-
Beta-blocker	281 (30.3)	-
ACE-inhibitor	155 (16.8)	-
ARB	1 (0.1%)	-
CCB	350 (37.9%)	-
Nitrate	475 (51.4%)	-
Nicorandil	7 (0.7%)	-
Statin	70 (7.6%)	-
Spironolactone	4 (0.4%)	-
Digoxin	34 (3.7%)	-
Warfarin	31 (3.4%)	-

Table 2.1: Baseline characteristics of post MI cohort.
[BP, blood pressure,; LVDD left ventricular diastolic diameter; SOB, breathlessness; ARB, angiotensin receptor blocker; CCB, calcium channel blocker]

Asymptomatic individuals took significantly fewer drugs than symptomatic subjects (1.6 ± 1.4 v 2.8 ±1.1 medications respectively, $p < 0.001$). Patients reporting breathlessness were over three times more likely to be taking a loop diuretic (27.4% v 8.9%, $p<0.001$) and twice as likely to be taking an ACE-inhibitor (20.2% v 11.4%, $p < 0.001$). Those reporting angina were more likely to be taking aspirin than those without (78.1% v 72.1%, $p = 0.002$), took more nitrates (65.8 % v 18.9%, $p < 0.001$) and calcium channel blockers (46.1% v 18.9%,

p<0.001). Beta-blocker use does not appear to have been influenced by symptoms; they were no more commonly prescribed in patients with angina compared to those without (30.8 v 29.9%, p = 0.79) those with breathlessness compared to those without (29.8 v 31.7%, p = 0.54), nor those who were symptomatic versus asymptomatic patients (30.4 v 31.2%, p 0.84).

Mean BMI was 27.5 ± 4.5 with a range of 16.5 to 48.0 (Figure 2.2). Approximately one quarter of the cohort (26.7%) had a BMI within the normal range and 2.6% were underweight. Almost one half (46.5%) were mildly obese whilst 22.6% were moderately obese. Fifteen individuals (1.6%) had a BMI in the severely obese range.

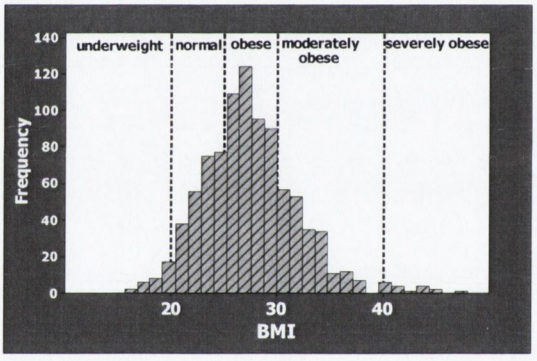


Figure 2.2: Histogram of BMI of post MI cohort

BMI tended to fall with increasing age (Pearson's co-efficient = -0.142, p <0.001). As expected, a higher BMI was associated with more co-morbidities; diabetics were heavier than non-diabetics (mean BMI 29.5 ±4.8 V 27.3 ± 4.4, p <0.001), and those with hypertension had a higher mean BMI than normotensives (28.0 ± 4.7 v 26.6 ± 4.0, p<0.001). Heavier patients were also more symptomatic; patients with angina had a higher mean BMI than angina-free individuals (27.8 ± 4.6 v 26.8 ± 4.2, p =0.002) and individuals reporting breathlessness had a higher mean BMI than non-breathless patients (27.8 ± 5.0 v 26.9 ± 3.6, p = 0.001)

2.3.1.2 ECHO findings

ECHO data was available for seven hundred and eighty eight patients. Of these, five hundred and seventy six (73.2%) were male and mean age was 61.2 ± 7.2 years. Figure 2.3 illustrates the distribution on LVEF within the cohort. Mean LVEF was 46.7 ± 12.4 % with a range of 11 - 76%.

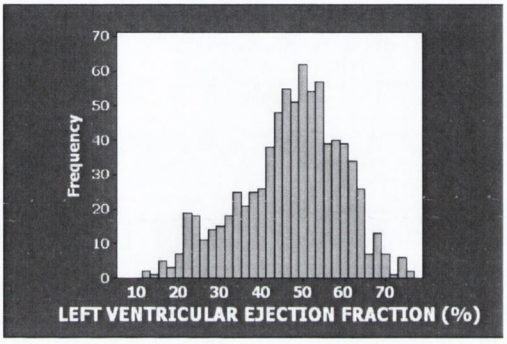


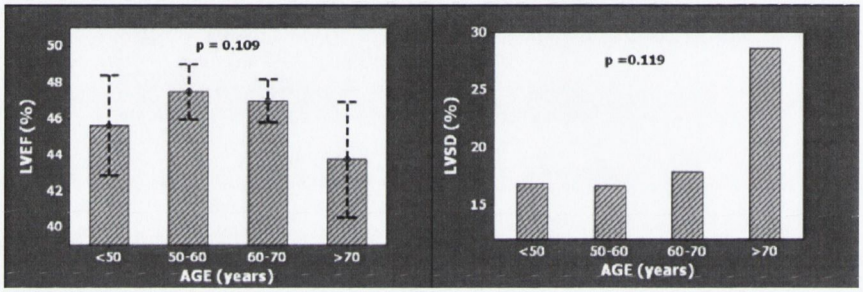
Figure 2.3: Histogram of LVEF of post MI cohort

Using the British Society of Echocardiography guidelines, only two hundred and fourteen patients (27.1%) had a LVEF in the normal range (EF > 55%). One hundred and forty six (18.5%) had severe LV systolic impairment (EF</= 35%), two hundred and seventy eight (35.3%) had mild LV systolic impairment (EF 45- 51%) and one hundred and fifty (19.0%) had moderate LV systolic impairment (EF 36 – 44%). However, for the purposes of our study only the one hundred and forty six individuals with an LVEF </=35% were defined as having left ventricular systolic dysfunction (LVSD). Thus, 15.8% of the entire post MI cohort had documented LVSD.

The distribution of LV end diastolic diameter (LVEDD) was normally distributed. Mean LVEDD was 5.4 ± 0.8cm with a range of 3.6 -9.0cm. Using BSE criteria for gender specific

normal range in LVEDD (>5.9cm for men, >5.3cm for women), 26.6% of the cohort exhibited LV dilatation. LVEDD correlated negatively with LVEF ($r = -0.567$, $p<0.001$).

Age did not have any significant association with LV function. LVEF did not correlate with age ($r = -0.015$, $p = 0.67$). Fig 2.4A and 2.4B indicate that there was a tendency toward lower LVEF and increased prevalence of LVSD in those individuals older than 70 years, but this did not reach statistical significance.



(A) (B)

Fig 2.4: Bar charts of age group versus mean LVEF (with 95% CI) and versus % LVSD

The baseline characteristics of those with LVSD compared with those without are detailed in Table 2.2. Unsurprisingly, those with LVSD were more likely to report breathlessness (65.8% v 55.5%, $p = 0.023$) although not more likely to report angina. Those with LVSD were prescribed slightly more medications per individual (2.8 v 2.5, $p = 0.019$); they were three times more likely to be taking a loop diuretic or ACE-inhibitor but were half as likely to be taking a beta blocker.

	LVSD		
	yes	no	p value
n	146	672	
male	124 (84.9)	453 (67.4)	<0.001
Age (years)	61.9 ± 7.3	61.1 ± 7.5	0.234
Hypertension	94 (67.1)	408 (60.7)	0.850
DM	19 (13.0)	62 (9.2)	0.165
LVDD (cm)	6.3 ± 0.9	5.2 ± 0.6	<0.001
Angina	93 (63.7)	453 (67.4)	0.388
SOB	96 (65.8)	373 (55.5)	0.023
Symptomatic	124 (84.9)	515 (76.6)	0.028
Medication			
Number of drugs	2.8 ± 1.4	2.5 ± 1.5	0.019
No medications	12 (8.2)	59 (8.8)	0.827
Thiazide	11 (7.5)	45 (6.7)	0.716
Loop	60 (41.1)	90 (13.4)	<0.001
Aspirin	114 (78.1)	492 (73.2)	0.224
Beta-blocker	23 (15.8)	225 (33.5)	<0.001
ACE-inhibitor	55 (37.7)	75 (11.2)	<0.001
CCB	46 (31.5)	248 (36.9)	0.218
Nitrate	71 (48.6)	321 (47.8)	0.850
Statin	6 (4.1)	53 (7.9)	0.110
Digoxin	11 (7.5)	13 (1.9)	<0.001
Warfarin	10 (6.8)	13 (1.9)	0.001

Table 2.2: Baseline characteristics of post MI cohort as function of LV function. Values are mean +/- SD, or numbers (%) as appropriate

2.3.1.3 Gender differences

A number of differences were seen between the genders at baseline: these are compared in Table 2.3. Women were significantly older than the men at screening, and had suffered their index MI almost three years later. Mean BMI and rates of hypertension and DM did not differ significantly between the genders.

	male	female	p value
n	677	247	
Age (years)	60.9 ± 7.6	62.7 ± 6.4	<0.001
Age at MI (years)	53.9 ± 7.3	56.2 ± 6.2	<0.001
Time from MI (years)	7.0 ± 2.4	6.6 ± 2.2	0.014
BMI	27.5 ± 4.1	27.5 ± 5.5	0.986
Height (cm)	168.9 ± 6.8	155.4 ± 6.0	<0.001
Weight (kg)	78.6 ± 13.6	66.4 ± 14.1	<0.001
Systolic BP (mmHG)	139.6 ± 23.4	140.9 ± 23.2	0.461
Diastolic BP (mmHG)	80.8 ± 13.0	78.1± 12.8	0.004
Pulse pressure (mmHG)	58.6 ± 18.2	62.6 ± 17.8	0.003
Hypertension	435 (65.2)	161 (67.6)	0.794
Diabetes Mellitus	73 (10.8)	27 (10.9)	0.949
LVSD	124 (18.3)	22 (8.9)	0.001
LVEF (%)	45.5 ± 12.5	50.0 ± 11.5	<0.001
LVDD (cm)	5.5 ± 0.8	5.0 ± 0.8	<0.001
Angina	458 (67.7)	186 (75.3)	0.025
SOB	394 (58.1)	169 (68.4)	0.005
Symptomatic	535 (79.0)	215 (87.0)	0.006
Medication			
Mean number of drugs	2.5 ± 1.5	2.8 ± 1.4	0.001
No medications	65 (9.6)	16 (6.5)	0.137
Thiazide	37 (5.5)	32 (13.0)	<0.001
Loop	110 (16.2)	76 (30.8)	<0.001
Aspirin	523 (77.3)	182 (73.7)	0.259
Beta-blocker	196 (29.0)	83 (33.6)	0.173
ACE-inhibitor	112 (16.5)	43 (17.5)	0.755
CCB	247 (36.5)	103 (41.7)	0.148
Nitrate	336 (49.6)	139 (56.3)	0.074
Statin	54 (8.0)	16 (6.5)	0.446
Digoxin	23 (3.4)	11 (4.5)	0.450
Warfarin	24 (3.6)	7 (2.8)	0.595

Table 2.3: Baseline characteristics of post MI cohort as a function of gender. Values are mean +/- SD, or numbers (%) as appropriate

Women were more symptomatic than men, being significantly more likely to report both angina and breathlessness. Perhaps as a result of this, women took significantly more medications per individual (2.8 v 2.5, p = 0.001) but this seemed to be almost exclusively in the form of diuretics; women were almost three times more likely to be taking a thiazide (13.3% v 5%, p<0.001) and twice as likely to be taking a loop diuretic (30.2% v 16.2%, p <0.001). The rate of anti-anginal, beta-blocker, ACE-inhibitor and aspirin did not vary between the genders.

LVEF was significantly lower in men (45.5 ± 12.5 v 50.0 ± 11.5, p <0.001) and men had a significantly higher rate of LVSD (18.3 v 8.9%, p <0.001). As expected, men had a higher mean LVEDD than women (5.5 ± 0.8 v 5.0 ± 0.8 cm, p<0.001) although the rate of LV dilatation between men and women was identical (26.8 v 26.8% respectively, p = 0.961).

2.3.1.4 Natriuretic peptides

Nine hundred and three individuals had NT-ANP levels recorded. Results were non-normally distributed (Fig 2.5A) and ranged from 0.2 to 127.2pg/ml, with a median value of 4.8pg/ml and IQ range of 4.4pg/ml. NT-ANP values became normally distributed following logarithmic transformation (Fig 2.5B). Eight hundred and seventy six patients had samples analysed for BNP. Results were again non-normally distributed (Fig 2.5C), ranging from 0.6 to 1919.0 pg/ml with a median value of 35.3pg/ml and IQ range of 56.7pg/ml. Three hundred and thirty (38.0%) patients had BNP levels >/= 50pg/ml with one hundred and fifty eight (18.0%) having BNP levels >/= 100pg/ml. Logarithmic transformation of BNP levels resulted in a normal distribution of results for the cohort (Fig 2.5D). Log BNP and log NT-ANP had a strong positive correlation (r = 0.668, p<0.001).

Higher natriuretic peptides levels with older age was demonstrated. Both BNP and NT-ANP had significant positive correlations with age (Table 2.4). Figure 2.6 demonstrates a stepwise increase in median NTP and BNP levels when the cohort was divided into categorical groups based on age. Natriuretic peptides showed no correlation with time from MI to screening. Natriuretic peptide levels were significantly higher in females than males, although this difference was more marked with BNP [median (IQR) 47.0 (67.7) v 32.0 (55.0) pg/ml, p

<0.001 respectively] than with NT-ANP [median (IQR) 5.1 (4.9) v 4.7 (4.2) pg/ml, p = 0.048 respectively].

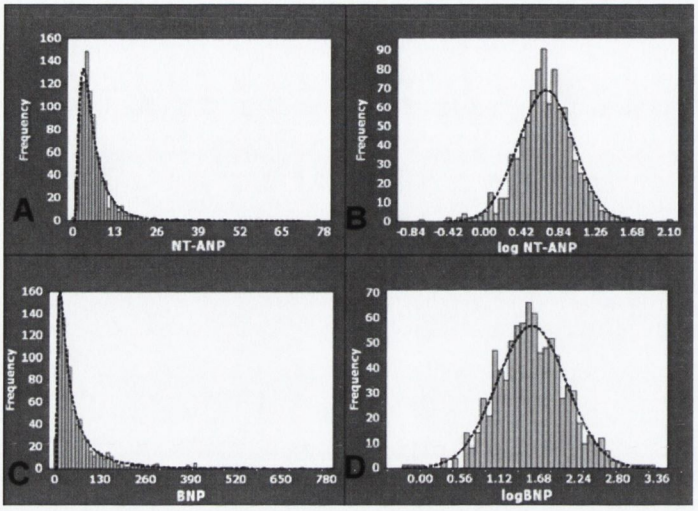


Figure 2.5: Histograms of natriuretic peptide distribution for post MI cohort. (A) NT-ANP distribution; (B) log NT-ANP; (C) BNP distribution; (D) log BNP. (Values on x axis for fig A and D is pg/ml.)

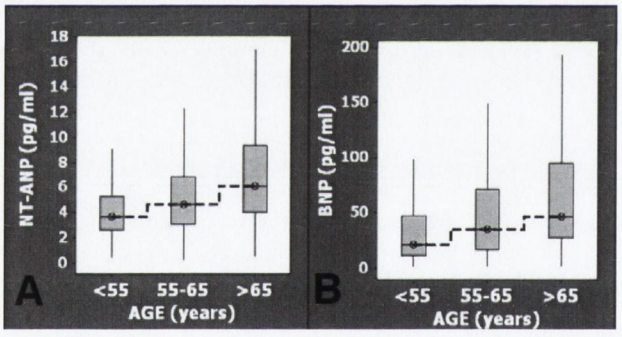


Figure 2.6: Boxplots of (A) NT-ANP and (B) BNP levels of post MI cohort when divided by age of less than 55 years old, between 55 and 65 years old and greater than 65 years old. (Dashed line = stepped median connect line.)

Hypertensives had higher median (IQR) levels of both BNP [38.3 (64.9) v 30.9 (50.5) pg/ml, p < 0.001] and NT-ANP [5.1 (4.7) v 4.4 (3.7) pg/ml, p <0.001) than normotensives. As shown in Table 2.4, both log BNP and log NT-ANP had weak but significant correlations with systolic blood pressure and pulse pressure but no correlation with diastolic blood pressure. There was no significant difference between diabetics and non-diabetics in median

(IQR) levels of BNP [40.0 (78.0) v 35.0 (56.0) pg/ml, p = 0.15] or NT-ANP [4.8 (4.9) v 4.6 (4.4) pg/ml, p =0.30].

Those individuals who reported breathlessness had higher BNP levels than non-breathless patients [38.3 (66.2) v 31.5 (47.0) pg/ml, p =0.017] but NT-ANP levels were similar [4.8 (3.8) v 4.7 (4.8) pg/ml]. Median (IQR) levels of BNP and NT-ANP were similar regardless of whether or not an individual reported angina (data not shown).

	Log BNP		Log NT-ANP	
	r =	p value	r =	p value
Age (years)	0.258	< 0.001*	0.302	< 0.001*
Time from MI (years)	0.029	= 0.339	0.045	= 0.173
LVEF (%)	-0.302	< 0.001*	-0.244	< 0.001*
LVEDD (mm)	0.352	< 0.001*	0.219	< 0.001*
Systolic BP (mmHG)	0.109	= 0.001*	0.133	< 0.001*
Diastolic BP (mmHG)	-0.035	= 0.305	0.006	= 0.859
Pulse Pressure (mmHG)	0.156	< 0.001*	0.170	< 0.001*
BMI	-0.112	< 0.001*	-0.091	= 0.006*
Height (cm)	-0.126	< 0.001*	-0.063	= 0.059
Weight (kg)	-0.163	< 0.001*	-0.112	= 0.001*

Table 2.4: Pearson's correlation coefficient of log BNP and log NT-ANP with continuous variables.

Both NT-ANP and BNP had close associations with LV structure and function. As shown in table 2.4, log BNP and log NT-ANP had significant correlations with LVEF. Those patients with LVSD had significantly higher median (IQR) NT-ANP [7.1 (8.1) v 4.4 (3.7) pg/ml, p<0.001] and BNP [93.0 (163.4) v 30.8 (57.4) pg/ml, p<0.001).

Figure 2.7 illustrates a ROC for the accuracy of the natriuretic peptides in identifying which of the cohort had LVSD. The AUCs for NT-ANP and BNP were 0.704 and 0.774 respectively.

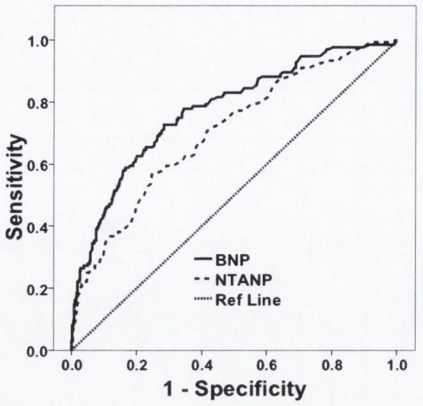


Figure 2.7: ROC curve for accuracy of NT-ANP and BNP for identifying LVSD.

Further assessment of the ability of BNP levels to identify LVSD in the cohort are demonstrated in Table 2.5, using differing cut-offs of BNP. As the cut-off level increased, sensitivity fell quickly but specificity was seen to increase. However, the negative predictive value fell as BNP cut-offs increased.

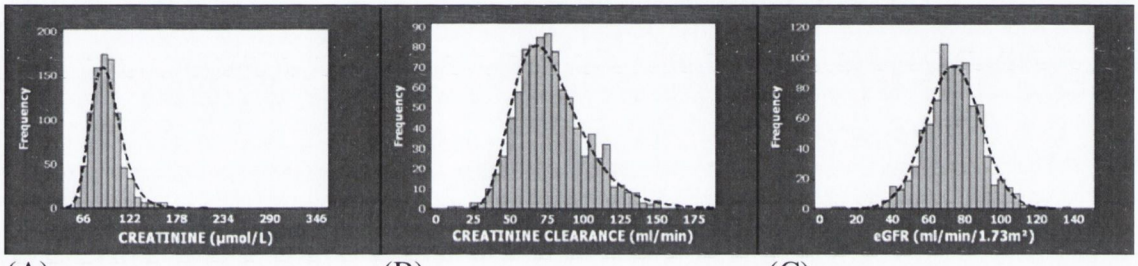
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
BNP > median	80.9	69.8	29.2	93.0
BNP > 50 pg/ml	72.2	56.9	34.7	92.0
BNP >75 pg/ml	58.8	82.7	43.0	90.1
BNP >100 pg/ml	47.0	88.0	46.3	88.2

Table 2.5: Power of differing cut-offs of BNP in identifying LVSD in post MI cohort

Similar associations were found between the natriuretic peptides and LV dilatation. Both NT-ANP and BNP had positive correlations with LVEDD (Table 2.4). Median (IQR) BNP levels were much higher in those patients with LV dilatation [89.9 (137.2) v 29.0 (39.4 pg/ml, p <0.001], as were NT-ANP levels [6.1 (5.1) v 4.5 (3.6) pg/ml, p<0.001) .As with LVSD, BNP proved more accurate than NT-ANP at identifying individuals with a dilated LV (ROC analysis: AUC 0.758 v 0.624).

2.3.2 Renal function

Eight hundred and ninety seven of the nine hundred and twenty four screened individuals had blood samples available for assessment of creatinine concentration. The distribution of serum creatinine, calculated creatinine clearance and eGFR are illustrated in figure 2.8. The baseline characteristics in terms of eGFR and serum creatinine are discussed in more detail below. Creatinine clearance was non-normally distributed, ranging from 8.9 to 165.8ml/min, with a median value of 74.7ml/min.



(A) (B) (C)

Figure 2.8: Renal function in the post MI cohort. Histograms of serum creatinine concentration (µmol/L), creatinine clearance (ml/min) and calculated eGFR (ml/min/1.73m²)

2.3.2.1 Estimated glomerular filtration rate

Calculated eGFR for the entire cohort was normally distributed (figure 2.8C). Mean eGFR was 73.2 ± 15.2 ml/min/1.73m² and ranged from 7.9 to 137.4 ml/min/1.73m². The number (percentage) of individuals with (i) eGFR > 90, (ii) eGFR 60 - 90, (iii) stage 3 CKD, (iv) stage 4 and (v) stage 5 or worse CKD was one hundred and three (11.5%), six hundred and thirty six (70.9%), one hundred and fifty five (17.3%), one (0.1%) and two (0.2%) respectively.

There was a significant difference between the genders in baseline renal function; males had significantly better renal function at baseline with a higher mean eGFR (75.6 ± 14.8

ml/min/1.73m² v 66.4 ± 13.9 ml/min/1.73m², p <0.001). As such, females had relatively increased representation in the CKD 2 and CKD 3+ groups (see Fig 2.9).

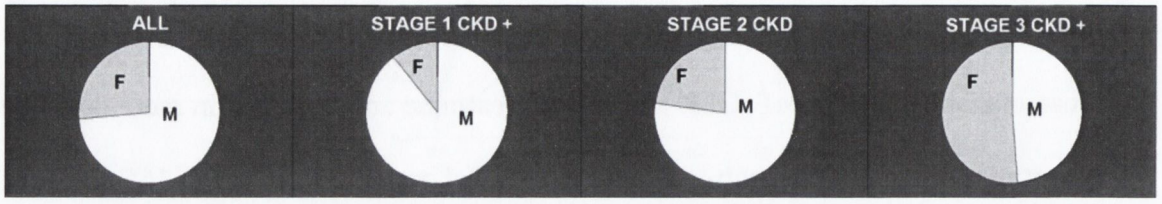


Figure 2.9: Distribution of gender per baseline CKD stage.
[F, female; M, male; stage 1 CKD +, eGFR > 90; stage 3 CKD -, stage 3 CKD or worse]

eGFR correlated negatively with age (r = -0.390, p <0.001, see Figure 2.10). There was no significant correlation between eGFR and LVEF (r = 0.011, p =0.76) and mean eGFR did not differ between those with LVSD and those without (71.7 ± 14.5 ml/min/1.73m² v 71.7 ± 16.5ml/min/1.73m², p =0.15). There was also no relationship between eGFR and LV size; eGFR did not correlate with LVEDD (r = 0.057, p = 0.19) and patients with a dilated LV had a similar mean eGFR to those with normal LV size (73.0 ±15.6 v 74.0± 15.0 ml/minj/1.73m², p = 0.53)

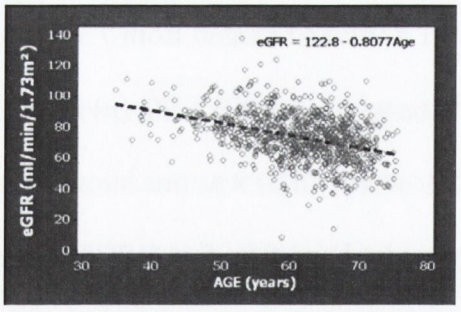


Figure 2.10: Scatterplot of eGFR v age in post MI cohort

There was no difference in mean eGFR between those with hypertension and normotensives (72.6 ±14.9 ml/min/1.73m² v 74.3 ± 15.5 ml/min/1.73m², p =0.13) nor between those with DM or those without (75.6 ± 16.3 ml/min/1.73m² v 72.9ml/minj/1.73m², p = 0.13). Table 2.6 reveals the baseline characteristics of the cohort when divided into CKD groupings. Only age

and gender differed significantly between the groups, with no difference in terms of hypertension, blood pressure, diabetes mellitus or BMI.

	ALL n = 924	eGFR >90 n = 103	eGFR 60 – 90 n = 636	CKD 3+ N = 158	p value
eGFR (ml/min/1.73m²)		>90	60-90	<60	
Mean age (yrs)	61.3 ± 7.3	56.9 ± 7.9	61.1 ± 7.1	65.4 ± 5.6	<0.001
Male (%)	73.2%	89.3%	77.2%	48.7%	<0.001
Time from MI (yrs)	6.9 ± 2.4	6.9 ± 2.2	6.9 ± 2.3	6.9 ± 2.6	0.970
Hypertension	64.5%	58.3%	65.1%	67.7%	0.279
SBP (mmHG)	139.9 ± 23.4	138.8 ± 20.9	140.5 ± 22.8	139.9 ± 26.5	0.788
DBP(mmHG)	80.1 ± 13.0	80.8 ± 12.3	80.6 ± 13.1	78.4 ±13.3	0.143
Diabetes mellitus	10.8%	17.5%	9.6%	10.7%	0.056
LVSD	15.8%	11.7%	16.2%	17.7%	0.295
LVEF (%)	46.7 ± 12.4	47.2 ± 11.3	46.6 ± 12.1	46.5 ± 14.2	0.908
BMI	27.5 ± 4.5	27.3 ± 4.6	27.5 ± 4.3	27.5 ± 4.9	0.952

Table 2.6: Baseline characteristics of post MI cohort as function of CKD status. Values are mean +/- SD, or numbers (%) as appropriate

Symptoms were more commonly reported in those with CKD 3 or worse, compared with those with better renal function. As illustrated in figure 2.11, breathlessness (SOB) was significantly more common (p = 0.017) and there was a tendency toward more self-reported angina (p=0.12). The proportion of patients who were "symptomatic", i.e. reporting angina and/or breathlessness, was significantly more common in those with CKD 3 or worse (p= 0.003).

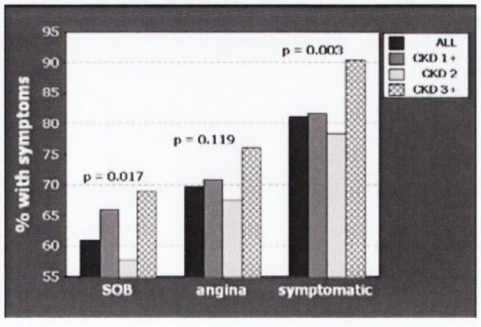


Fig 2.11: Barchart of reported symptoms per CKD stage

Table 2.7 shows the distribution of prescribed medication per CKD group. Those with worse renal function at baseline were more likely to be taking an ACE-inhibitor, a diuretic or digoxin. Anti-anginal prescription, including beta-blocker, did not vary according to renal function and there was no difference between CKD groups in statin or aspirin prescription.

	All n = 924	eGFR >90 n = 103	eGFR 60 - 90 n = 636	CKD 3 + n = 158	p value
ACE-I	155 (16.9)	10 (9.7)	92 (14.5)	48 (30.4)	<0.001
B blocker	281 (30.4)	31 (30.1)	201 (31.6)	42 (26.6)	0.469
Diuretic	255 (27.6)	10 (9.7)	159 (25)	78 (49.4)	<0.001
Aspirin	705 (76.3)	81 (78.6)	488 (76.7)	118 (74.7)	0.752
Statin	70 (7.6)	8 (7.8)	51 (8)	10 (6.3)	0.775
Nitrate	475 (51.4)	53 (51.5)	320 (50.3)	89 (56.3)	0.400
CCB	350 (37.9)	40 (38.8)	245 (38.5)	56 (35.4)	0.762
Digoxin	34 (3.7)	0 (0)	19 (3)	13 (8.2)	0.001
Warfarin	31 (3.4)	1 (1)	21 (3.3)	8 (5.1)	0.198

Table 2.7: Prescribed drugs per CKD stage. Values are number (%).

2.3.2.2 Serum creatinine

Creatinine levels were non-normally distributed (Figure 2.8A); median creatinine was 90.9 μmol/L, ranged from 55.6 to 666.0 μmol/L and had an interquartile range of 20.6μmol/l. The distribution of creatinine became normal following logarithmic transformation. Table 2.8 shows the baseline characteristics of the cohort as a function of baseline serum creatinine categories as used elsewhere (43,79). Only three individuals (0.33%) of the cohort had "markedly elevated" serum creatinine, with one hundred and forty eight (16.5%) having "mildly elevated" creatinine; the remaining seven hundred and forty six patients had "normal" creatinine.

Increasing age was associated with a higher creatinine; log creatinine correlated significantly with age ($r = 0.186$, $p < 0.001$). Median creatinine concentration was much higher in men (94.5μmol/L v 80.6 μmol/L, $p < 0.001$) although median creatinine did not vary between those

with hypertension and those without (91.7 (21.4) v 90.2 (20.2) μmol/l, p = 0.25) nor between those with diabetes mellitus and those without (89.9 (24.5) v 90.9(20.4) μmol/l, p = 0.50).

Creat (μmol/l)	Normal < 106	Mildly elevated 106 -177	Markedly elevated >177	p value normal v mild
n	746	148	3	-
Mean age (yrs)	60.6 ± 7.3	65.1 ± 6.0	62.5 ± 3.7	< 0.001
Male (%)	531 (71.1)	126 (85.1)	3 (100)	< 0.001
Time from MI (yrs)	6.8 ± 2.3	7.2 ± 2.5	8.3 ± 2.4	0.093
Age at MI	53.8 ± 7.1	57.9 ± 5.7	54.3 ± 3.2	< 0.001
Hypertension	63.8%	69.6%	66.7%	0.178
SBP (mmHG)	140.1 ± 22.7	139.7 ± 25.9	167.3 ± 40.1	0.835
DBP(mmHG)	80.5 ± 12.9	78.6 ± 13.7	92.0 ± 17.6	0.113
Diabetes mellitus	11.3	8.1%	0%	0.258
BMI	27.5 ± 4.5	27.4 ± 4.2	23.6 ± 1.9	0.791
LVSD	107	34	2	0.009
LVEF (%)	47.3 ± 11.9	43.8 ± 14.3	25.5 ± 7.7	0.012
LVDD	5.4 ± 0.8	5.6 ± 0.8	4.9	0.100
Angina	68.6%	73.7%	66.7%	0.226
SOB	60.7%	59.5%	100%	0.797
symptomatic	80.3%	84.5%	100%	0.253
Medications				
ACE-I	109 (14.6%)	40(27.0%)	1(33.3%)	<0.001
B blocker	232 (31.1%)	40 (27.0%)	2 (66.7%)	0.316
Diuretic	183 (24.5%)	63 (42.5%)	1 (33%)	<0.001
Aspirin	669 (76.9 %)	111(75.0%)	2 (66.7%)	0.277
Statin	64 (8.5%)	6 (4.0%)	0 (0%)	0.061

Table 2.8 Baseline characteristics of post MI cohort as function of renal function based on serum creatinine.

Unlike eGFR, there was an association between LV function and serum creatinine. Those individuals with LVSD had a significantly higher median creatinine (94.1 (22.3) v 90.6 (20.2) μmol/l), p = 0.002) than those with normal systolic function, and log creatinine correlated negatively with LVEF (r = -0.126, p <0.001) and positively with LVEDD (0.149, p =0.001).

2.3.2.3 Comparing creatinine and eGFR

The absolute number of subjects who had abnormal creatinine (n = 151) is similar to those with CKD stage 3 or worse based on eGFR (n = 158), suggesting that both methods of assessing renal impairment achieved comparable results. However, fifty one (33.7%) of those with mildly or markedly elevated creatinine actually had eGFRs greater than 60ml/min/1.73m^2. Conversely, fifty nine (37.3%) of those with CKD stage 3 or worse had serum creatinine levels in the normal range (>106μmol/l).

This latter group of fifty nine patients (6.6% of entire cohort) would thus have been misclassified as having "normal renal function" even though their eGFR was significantly reduced at < 60ml/min/1.73m^2. This group was exclusively female and older than the mean (64.1 ± 6.1 years) by approximately three years. The rate of hypertension (69.5%) and diabetes mellitus (15.0%) in this misclassified group was higher than that in the entire cohort, but LV function was better, with mean LVEF of 51.9 ± 4.8% and a rate of LVSD of only 5.1%.

Taking a calculated eGFR of <60ml/min/1,73m^2 as the gold standard marker of renal impairment, we can assess how accurate serum creatinine is at identifying these patients, as illustrated in a ROC curve in figure 2.12.

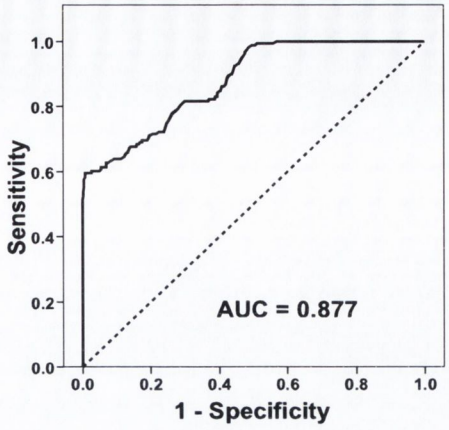


Figure 2.12: ROC curve assessing ability of serum creatinine level to identify patients with renal impairment (defined as eGFR < 60ml/min/1.73m²)

Table 2.9 illustrates the accuracy of using a serum creatinine of >106μmol/l in identifying renal impairment in the entire cohort. Overall, sensitivity is high at 92.1% but it is non specific at 65.6%. Serum creatinine is a very sensitive identifier of renal impairment in men, but not so in women. This cut-off was a more sensitive test in the younger patients, but less specific. Using ROC analysis, the AUC for identifying renal impairment with serum creatinine was 0.882 for those older than the mean, and 0.855 for those younger than the mean.

	sensitivity	specificity	PPV	NPV
All	92.1%	65.6%	92.9%	62.6%
Male	100%	62.1%	91.1%	100%
Female	72.5%	100%	100%	27.1%
Age < mean	94.5%	53.9%	95.0%	51.2%
Age > mean	89.8%	69.7%	90.9%	66.6%

Table 2.9: Ability of using a cut-off of serum creatinine of >106μmol/l in identifying renal impairment (defined as eGFR <60ml/min/1.73m²)

2.3.2.4 Renal function and natriuretic peptides

Lower renal function had a strong association with elevation of natriuretic peptides. eGFR had significant negative correlations with both log NT- ANP ($r = -0.329$, $p < 0.001$) and log BNP ($r = -0.213$, $p < 0.001$). Figure 2.13 illustrates how the natriuretic peptide levels increased in a step wise manner as CKD stage declined.

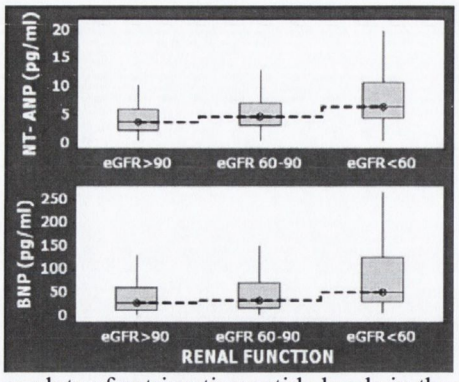


Figure 2.13: Box-plots of natriuretic peptide levels in the post MI cohort based on baseline CKD stage.

Log creatinine correlated significantly with both log BNP ($r = -0.322$, $p < 0.001$) and log NT-ANP ($r = -0.246$, $p < 0.001$).

2.3.2.5 Renal function and LVSD

Taking a eGFR of e >60ml/min/m^2 as "normal renal function" and eGFR below this level as having CKD, the cohort was then divided in to four groups: (i) those with normal kidney function and normal LV systolic function (n = 531): (ii) those with CKD alone (n = 99): (iii) those with LVSD alone (n =115) and; (iv) those with both CKD and LVSD (n = 28). Table 2.10 shows the baseline characteristics of these groups.

These four groups did not differ in the proportion of individuals with hypertension or diabetes mellitus, and mean BMI, systolic blood pressure or diastolic blood pressure was similar in all four groups. Although reported angina was similar between the groups, those with both LVSD and CKD were more likely to report breathlessness than those with LVSD alone (82.1% v 62.6%).

	LVSD - CKD -	LVSD - CKD +	LVSD + CKD -	LVSD + CKD +	p value
Mean age	60.2 ± 7.2	65.1 ± 6.0	61.2 ± 7.7	64.8 ± 5.9	< 0.001*
% male	76.3	89.3	87.9	75	< 0.001*
BMI	27.1 ± 4.1	27.5 ± 4.6	27.4 ± 4.6	27.0 ± 5.2	0.767
HTN (%)	62.3	72.7	65.8	53.5	0.129
DM (%)	9.2	12.1	14.8	7.1	0.284
Systolic BP(mmHG)	139.5 ± 22.2	142.6 ± 24.4	141.2 ± 23.8	132.0 ± 30.2	0.169
Diastolic BP(mmHG)	80.1 ± 12.8	79.3 ± 13.1	82.5 ± 13.8	76.6 ± 14.3	0.112
Angina (%)	68.9	78.7	62.6	67.9	0.084
SOB (%)	56.3	66.6	62.6	82.1	0.013*
Medications					
ACE-Inhibitor (%)	9.4	24.2	23.2	60.7	< 0.001*
Diuretic (%)	16.8	42.4	42.6	78.5	< 0.001*
Beta blocker (%)	36.1	29.2	15.6	17.6	< 0.001*
Statin (%)	8.2	9.0	5.2	0	< 0.274
CCB (%)	38.8	38.3	32.1	28.5	0.431
Aspirin (%)	76.3	78.8	79.1	75	0.813
Mean number of meds	2.3 ± 1.3	2.8 ± 1.6	2.6 ± 1.5	3.6 ± 1.3	< 0.001*

Table 2.10: Baseline characteristics of post MI cohort as divided by presence or absence of CKD and/or LVSD

Individuals with both LVSD and CKD took significantly more medications than the others, and this seem to have been predominantly due to ACE-inhibitors and diuretics. These individuals were almost three times as likely to be taking an ACE-inhibitor than those people with LVSD and normal kidney function (60.7% v 23.2%) and six times more likely to be taking one compared to individuals with normal renal function and LV function (60.7% v 9.4%). Similarly, people with both LVSD and CKD were almost twice as likely to be taking a diuretic as those with LVSD alone (78.5% v 42.6%) and those with CKD alone (78.5% v 42.4%), and over four times more likely than those with normal renal and LV function. Beta blocker use in those with LVSD and CKD was half that seen in those with normal renal and cardiac function (17.6% v 36.1%)

Figure 2.14 reveals how the presence of LVSD and/or CKD leads to increasing levels of natriuretic peptides.

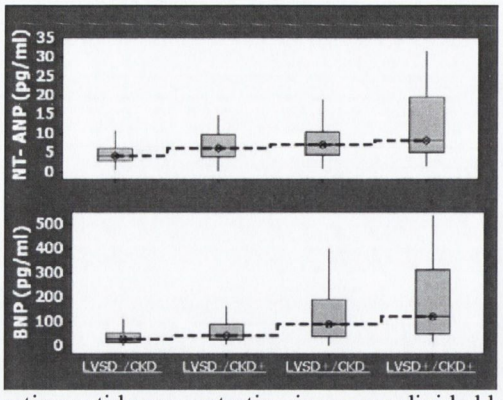


Figure 2.14: Box plot of natriuretic peptide concentration in groups divided by presence or absence of CKD and/or LVSD

2.3.3 Outcome

All deaths were recorded up to and including the 31st December 2006. Mean follow-up was for 11.0 ± 0.4 years. Of the nine hundred and twenty four individuals recruited to the study, three hundred and two (32.7%) had died by this date. As demonstrated in figure 2.15, the rate of death was linear throughout the follow up period.

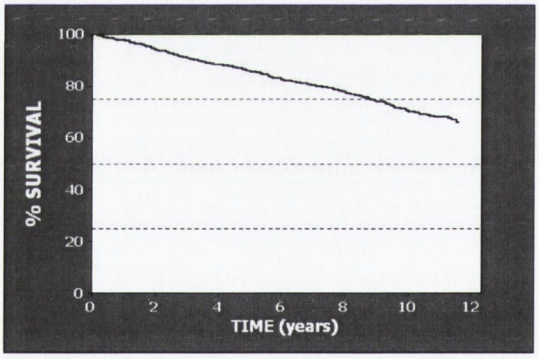


Figure 2.15: Kaplan-Meier curve of survival of post MI cohort during follow up period

The deaths were coded thus:

- Cardiovascular deaths 197 (65.2% of all deaths)
- Cancer deaths 56 (17.5%)
- Respiratory deaths 27 (8.9%)
- Other 16 (5.3%)
- Uncoded 6 (2.0%)

Of the cardiovascular deaths, one hundred and twelve (56.8%) were attributed to a MI, twenty five (12.7%) to HF and fourteen (7.1%) to a cerebrovascular accident. Thirty five (17.7%) had "ischaemic heart disease" listed as the primary cause of death with the remaining eleven individuals having another cause of cardiovascular death listed, for example, cardiogenic shock.

Of the deaths attributed to cancer, lung was the commonest site with twenty four (42.8%). Ten (17.8%) had a gastro-intestinal malignancy, six (10.7%) had cancer of the urogenital tract and three (5.3%) died of breast cancer. Twelve (21.4%) individuals died of malignancy where the primary source was unknown or not detailed in the death certificate.

2.3.3.1 All cause mortality

Figure 2.16 illustrates Kaplan-Meyer curves of survival for the cohort over the follow up period, divided by a variety of categorical measurement. Male and female patients had a similar all cause mortality rates throughout the follow up period (Fig 2.16A). Hypertensives (Fig 2.16B) and diabetics (Fig 2.16C) had significantly higher mortality rates than normotensives and non-diabetics respectively. In terms of BMI and outcome, those who were underweight or severely overweight had the worst outcome (Fig 2.16D), with respective crude mortality rates of 41.7% and 40%; this compares with a crude mortality rate of 31.6% for those with a BMI between 25 and 30.

When the cohort was divided based on LV systolic function as per BSE guidelines, those with severe LVSD (EF <35%) had by far the worst outcome (Fig 2.16E), with a crude mortality rate of 55.5%. Those with normal LV function, mild LVSD and moderate LVSD had very

similar outcome, with mild LVSD actually having a slightly lower mortality rate than normal LV function (23.3% v 26.0% respectively). Figure 2.16F illustrates outcome based on the definition of LVSD used in this study. Angina was not associated with increased mortality rates (Fig 2.16G) although breathlessness (Fig 2.16H) was. Aspirin did not appear to influence outcome (Fig 2.16I), although both statin (Fig 2.16L) and beta-blocker use (Fig 2.16K) were associated with lower mortality rates. ACE-inhibitor use was associated with poorer long term outcome but this is likely due to the confounding influence of LVSD. Increasing age was strongly associated with increased mortality; crude mortality for those aged greater than the mean was much higher than for those under the mean age (41.3 v 24%, $p < 0.001$)

2.3.3.2 Cardiovascular Death

Figure 2.17 demonstrates Kaplan-Meier curves for cumulative cardiovascular death over the follow up period for a variety of categorical variables. Cardiovascular death rates followed similar patterns to all cause mortality. Male and females had similar (Fig 2.17A) outcomes with hypertensives (Fig 2.17B) and diabetics (Fig 2.17C) having poorer outcomes. LVSD was associated with a higher rate of cardiovascular death (Fig 2.17E and 2.17F) as was breathlessness (Fig 2.17H). Although the cumulative cardiovascular death curves for angina v no angina do appear to separate (Fig 2.17G), there was no statistically significant difference.

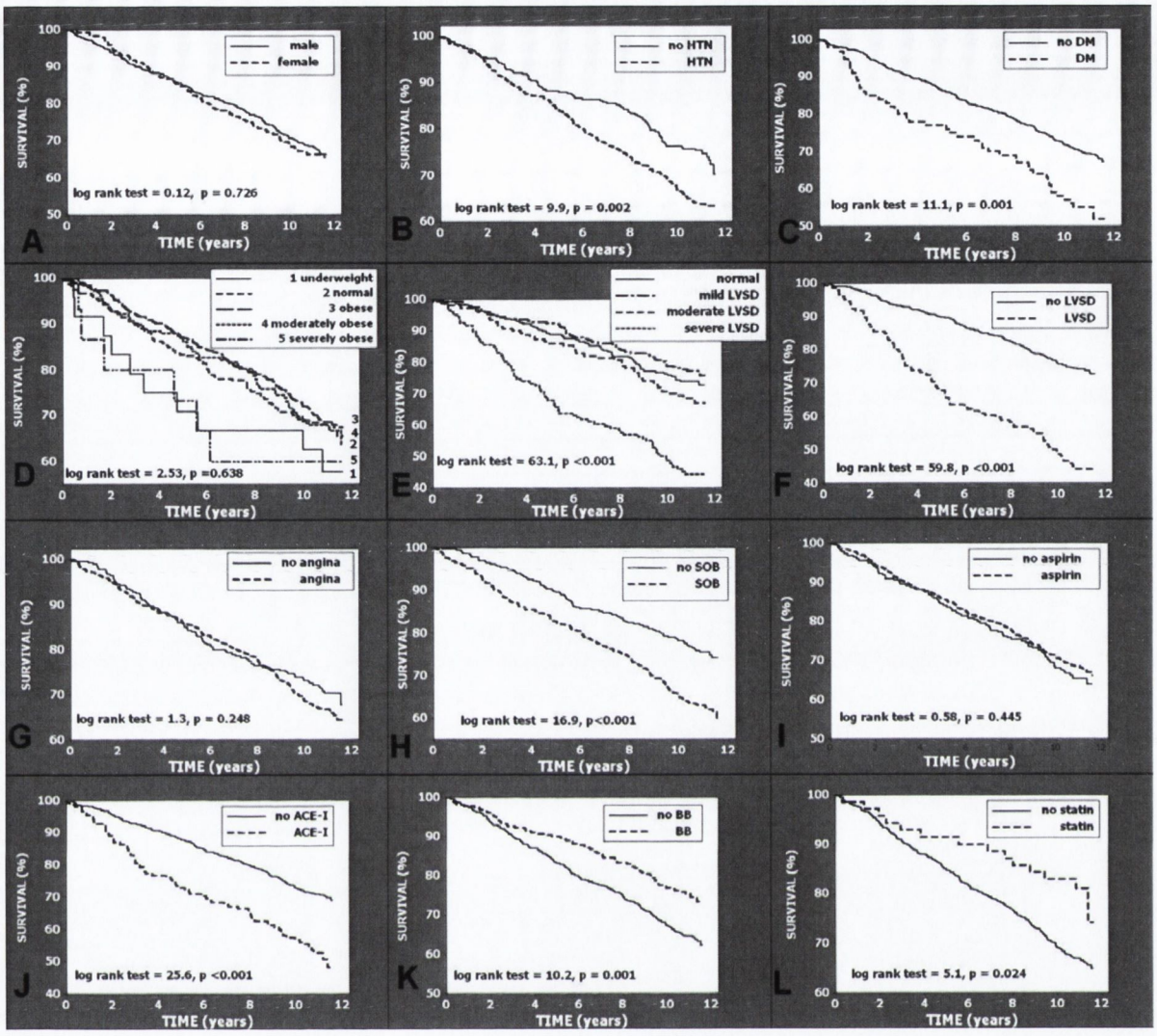


Figure 2.16: Kaplan Meyer survival curves: All Cause Mortality in post MI cohort.
Graphs indicate influence of: (A) gender; (B) hypertension; (C) Diabetes Mellitus; (D) BMI; (E) LV function as per BSE guidelines; (F) LV function as per study definition; (G) angina; (H) breathlessness; (I) aspirin use at screening; (J) ACE-inhibitor use at screening; (K) beta-blocker use at screening and; (L) statin use at screening.

Aspirin use showed a slightly lower (but not significant) cardiovascular death rate (Fig 2.17I) compared to those not taking aspirin (respective crude cardiovascular death rates, 32.0% v 34.7%). As with all cause mortality, beta-blocker use was associated with a significantly lower rate of cardiovascular death (Fig 2.17K), although statin use did not appear to influence this (Fig 2.17L). ACE-inhibitor use was associated with increased cardiovascular deaths (Fig 2.17J). Increasing age was associates with higher rates of cardiovascular death; crude

mortality for those over the median age was significantly higher than for those under the median (26 v 16.7%, p = 0.001).

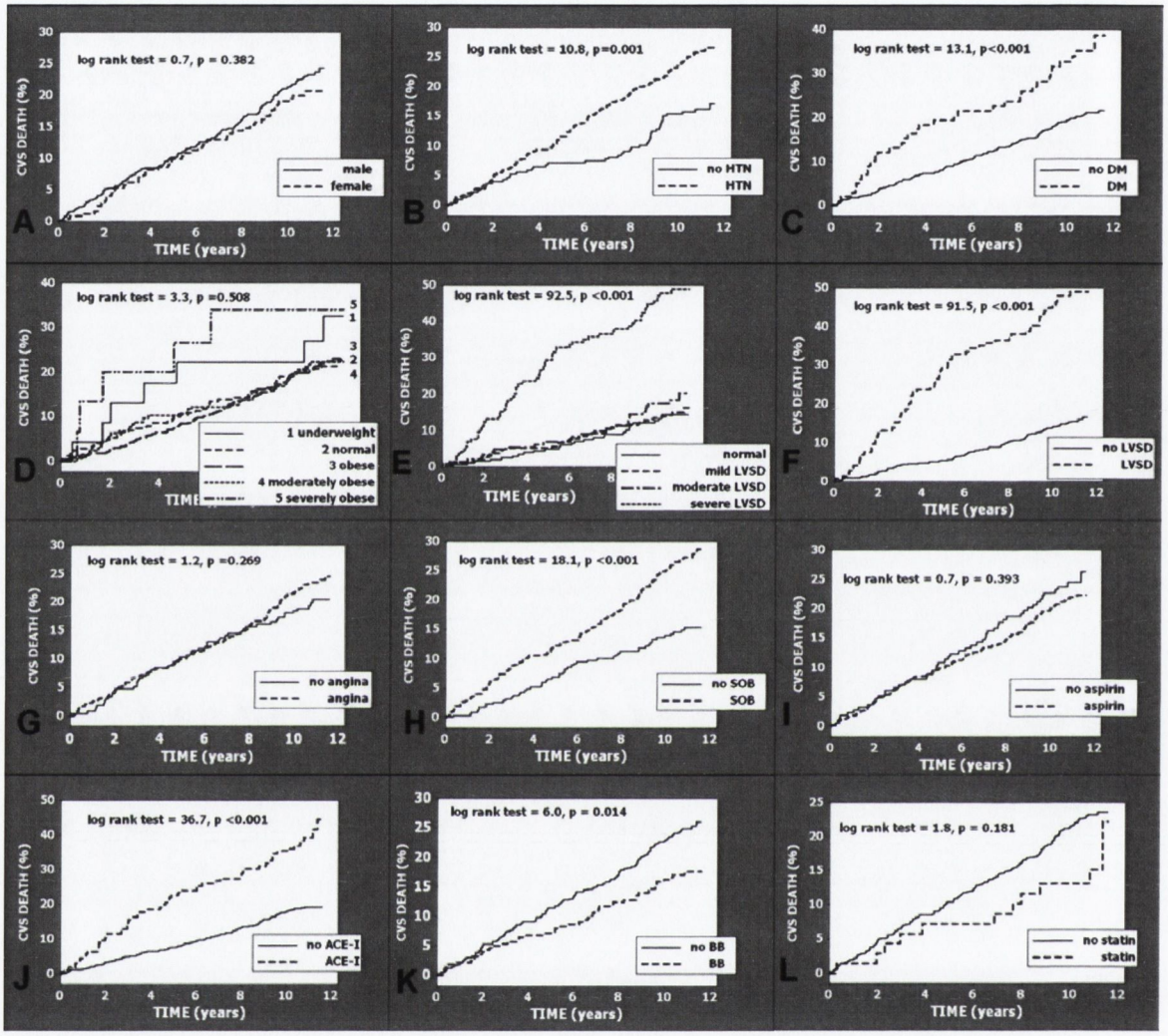


Figure 2.17: Kaplan Meyer cumulative failure curves: Cardiovascular Deaths in post MI cohort. Graphs indicate influence of: (A) gender; (B) hypertension; (C) Diabetes Mellitus; (D) BMI; (E) LV function as per BSE guidelines; (F) LV function as per study definition; (G) angina; (H) breathlessness; (I) aspirin use at screening; (J) ACE-inhibitor use at screening; (K) beta-blocker use at screening and; (L) statin use at screening.

2.3.3.3 Cox Regression

Univariate hazard ratios (HR) for all cause mortality and cardiovascular death are summarized in Table 2.11. Increasing age was associated with increased risk of poor outcome; being older than 65 years old carried unadjusted HRs of 2.65 (1.80- 3.80) for all

cause mortality and 2.53 (1.61 – 4.00) for cardiovascular death, compared to people age 55years old or younger.

	All cause mortality			Cardiovascular death		
	HR	95% CI	p value	HR	95% CI	p value
Male	0.96	0.74 – 1.23	0.726	1.16	0.83 – 1.61	0.382
Age[1]	1.06	1.04 – 1.08	<0.001	1.05	1.03 – 1.08	<0.001
BMI[1]	0.99	0.967 – 1.02	0.498	1.00	0.96 – 1.03	0.927
DM	1.70	1.24 – 2.32	0.001	1.96	1.35 – 2.83	<0.001
HTN	1.49	1.16 – 1.92	0.002	1.70	1.23 – 2.33	<0.001
LVSD	2.73	2.09 – 3.56	<0.001	4.09	3.00 – 5.60	<0.001
LVEF[1]	0.97	0.96 – 0.98	<0.001	0.95	0.94 – 0.96	<0.001
LVEDD[1]	1.77	1.48 – 2.11	<0.001	2.30	1.89 – 2.80	<0.001
Angina	1.16	0.90 – 1.49	0.249	1.19	0.87 – 1.64	= 0.453
SOB	1.67	1.30- 2.14	<0.001	1.96	1.43 – 2.70	<0.001
Medications						
ACE-I	1.94	1.49 -2.51	<0.001	2.49	1.84 – 3.39	<0.001
Beta blocker	0.65	0.50 – 0.85	0.002	0.67	0.48 – 0.92	0.015
Statin	0.54	0.32 – 0.93	0.026	0.66	0.36 – 1.21	0.184
Aspirin	0.90	0.70 – 1.17	0.446	0.87	0.63 – 1.20	0.393

Table 2.11: Univariate HR for all cause mortality and cardiovascular death for different variables ([1]continuous variable)

The strongest univariate predictor of both all cause mortality and cardiovascular death was LVSD, and both LVEF and LVEDD had significantly positive HRs. ACE-inhibitors were strong univariate predictors of both all cause mortality and cardiovascular death, whilst beta blockers were predictive of better long term outcome. Statin use predicted good long term outcome with regards to all cause mortality, but had no significant association with cardiovascular death ($p = 0.18$)

All variables with univariate HR with p values <0.1 were included in the final model for multivariate analysis. The results of this are shown in table 2.12. Following multivariate adjustments, hypertension, diabetes mellitus, age and LVSD all remained strong predictors of poor outcome. Breathlessness was also a strong independent predictor of poor outcome. Beta blocker use and statin use were no longer predictors of outcome following multivariate

analysis although ACE-inhibitor use remained an independent predictor of both all cause mortality and cardiovascular death.

	All cause mortality			Cardiovascular death		
	HR	95% CI	p value	HR	95% CI	p value
Age[1]	1.07	1.05 – 1.09	<0.001	1.06	1.04 – 1.09	<0.001
DM	1.63	1.14 – 2.32	0.007	1.76	1.16 – 2.66	0.007
HTN	1.54	1.16 – 2.04	0.003	1.75	1.25 – 2.51	0.002
LVSD	2.28	1.73- 3.01	<0.001	3.30	2.38 – 4.58	<0.001
SOB	1.54	1.16 – 2.04	0.002	1.86	1.31 – 2.66	<0.001
ACE-I	1.65	1.22 – 2.21	0.001	2.03	1.43 – 2.89	<0.001
BB	0.88	0.64- 1.19	0.399	1.00	0.68 – 1.47	0.992
Statin	0.83	0.49 – 142	0.487	-	-	-

Table 2.12: Multivariate HR for all cause mortality and cardiovascular death
[Co-variates in final model: ACM = LVEF, age, DM, HTN, BB, SOB, statin, ACE
CVS = LVEF, age, HTN, DM, ACE, Beta- blocker, SOB]

2.3.3.4 Natriuretic peptides and outcome

Figure 2.18 illustrates long term survival and rate of cardiovascular death when the cohort was divided based on baseline natriuretic peptide quartile (quartile 1 having the lowest levels). With BNP, a step-wise increase in mortality was seen with higher quartile (fig 2.18A and 2.18B). Compared to the lowest BNP quartile, the fourth BNP quartile had univariate HRs of 2.99 (2.09 – 4.27) for all cause mortality and 3.76 (2.40 – 5.90) for cardiovascular death. Following multivariate analysis, these values remained statistically significant at 2.04 (1.30- 3.22) and 2.66 (1.42 – 4.97) respectively.

LogBNP had univariate HRs of 2.82 (2.21- 3.60) for all cause mortality and 3.54 (2.62 – 4.78) for cardiovascular death. On multivariate analysis, adjusted HRs were 2.00 (1.46 – 2.75) and 2.18 (1.47 – 3.23) respectively.

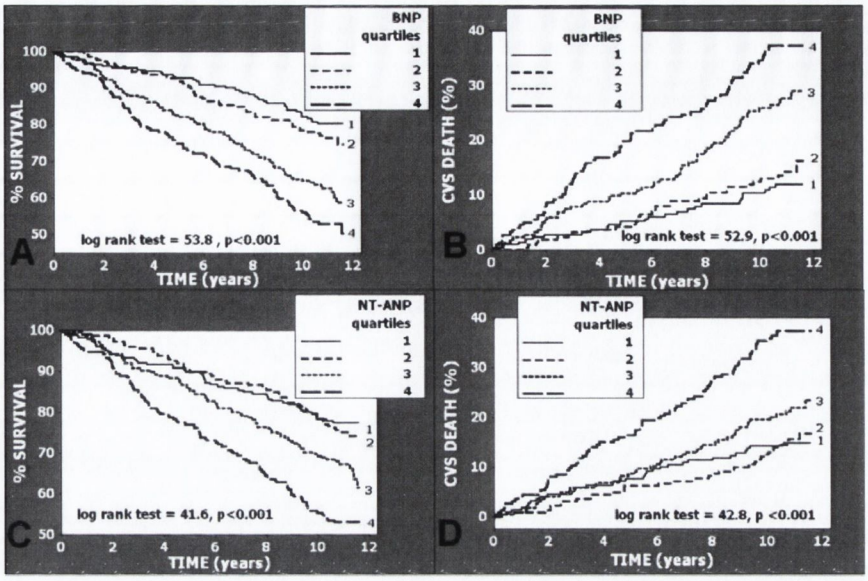


Figure 2.18: Kaplan-Meier curves of outcome as a function of baseline natriuretic peptide levels. (A) survival per BNP quartile, (B) cumulative CVS death rate per BNP quartile, (C) survival per NT-ANP quartile, (D) cumulative CVS death rate per NT-ANP quartile.

Figure 2.18C and 2.18D illustrate baseline NT-ANP quartiles and long term outcome. Survival and cardiovascular death rates in quartiles 1 and 2 had very similar patterns, although quartiles 3 and 4 exhibited significantly higher levels of adverse events. Compared to the lowest NT-ANP quartile, the fourth quartile had univariate HRs of 2.48 (1.77- 3.45) for all cause mortality and 2.89(1.92 – 4.26) for cardiovascular death. Following multivariate analysis, these values were 1.90 (1.27 – 2.85) and 2.35 (1.40 – 3.95) respectively. The unadjusted HRs for log NT-ANP for all cause mortality was 4.14 (2.82- 6.09) and 5.41 (3.38 – 8.68) for cardiovascular death; these HRs, when adjusted following multivariate analysis, were 2.74 (1.70 – 4.42) and 3.45 (1.9 – 6.26) respectively

2.3.4 Renal function and outcome

Low renal function was associated with poorer outcome.

2.3.4.1 eGFR/CKD classification and outcome

Fig 2.19A and 2.19B illustrate survival and cardiovascular death rate based on CKD classification. Patients with an eGFR lower than 60ml/min/m^2 had much worse outcomes than those with CKD stage 2 or those CKD stage 1 or better. Indeed, the latter two groups had similar outcomes. It appears than as eGFR declined, increased mortality was only seen once eGFR fell below 60ml/min/m2. Figure 2.19C and 2.19D reveal that outcome was largely unchanged regardless of whether baseline eGFR was between 60 and 70ml/min/m^2, between 70 and 80 ml/min/m^2, between 80 and 90ml/min/m^2 or above 90 ml/min/m^2.

However, once eGFR was below 60ml/min/m^2, it seems that all cause mortality and cardiovascular death rate increased significantly as eGFR fell. Figures 2.19E and 2.19F illustrate that outcome was much worse for those with eGFR between 50 and 60ml/min^2 compared to those with eGFR >60ml/min/m^2, and that those with an eGFR <50ml/min/m^2 had the worst outcome of all.

Death coding per CKD status is demonstrated in table 2.13. The higher overall mortality in CKD stage 3 was largely due to a higher rate of cardiovascular deaths. The proportion of deaths due to malignancy was similar in all groups. The crude mortality rates due to MI, HF and stroke were all higher in the CKD stage 3 group; the proportion of cardiovascular deaths due to MI was similar between all 3 groups, although the proportion of cardiovascular deaths due to HF was much higher in CKD stage 3.

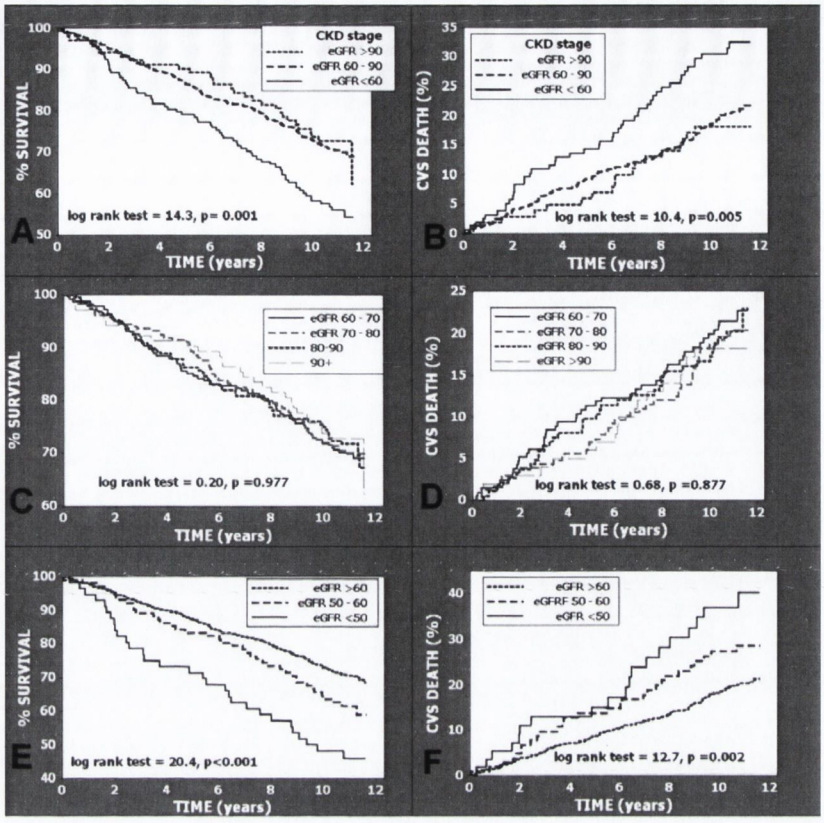


Figure 2.19: Kaplan-Meier curves of long term outcome as function of baseline renal function. (A) Survival per CKD stage, (B) cumulative CVS death rate per CKD stage, (C) Survival per 10 point fall in eGFR in those with eGFR > 60, (D) cumulative CVS death rate per 10 point fall in eGFR in those with eGFR > 60, (E) Survival per 10 point fall in eGFR in those with eGFR < 60, (F) cumulative CVS death rate per 10 point fall in eGFR in those with eGFR < 60.

	eGFR > 90	eGFR 60 - 90	CKD 3
N	103	636	158
Crude mortality (%)	28.2	29.9	44.3
Cause of death (%)			
Cardiovascular	61.2	66.2	67.0
Cancer	17.3	17.7	17.2
Respiratory	10.3	5.4	4.3
Other	10.3	8.4	9.9
Crude mortality (%) due to			
Myo Infarction	10.7	11.5	15.8
Heart Failure	1.0	2.2	6.3
CVA	0.0	1.4	3.5
Other	5.8	4.7	5.1
Cause of CVS death (%)			
Myo Infarction	61.1	58.1	53.2
Heart Failure	5.7	11.1	21.1
CVA	0.0	7.1	11.9
Other	33.1	23.7	17.1

Table 2.13: Death coding per CKD stage

eGFR, assessed as a continuous variable, was a univariate predictor of all cause mortality [HR 0.99 (0.98- 0.99)] and also of cardiovascular death [0.99 (0.98 – 0.99)]. However, following multivariate analysis, it proved not to be an independent predictor of outcome; adjusted HR for all cause mortality 1.0 (0.99 – 1.01), p = 0.772; adjusted HR for cardiovascular death 0.99 (0.99 – 1.01) p=0.615.

Similarly, CKD stage 3 or worse (eGFR<60ml/min/m²) was a univariate predictor, but not an independent predictor of both all cause mortality and cardiovascular death (table 2.14), compared to an eGFR >90ml/min/m².

	All cause mortality		**Cardiovascular death**	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
eGFR > 90 ml/min/m²	1.0	1.0	1.0	1.0
eGFR 60 -90 ml/min/m²	1.08 (0.73 – 1.60)	1.13 (0.72 – 1.78)	1.15 (0.70 – 1.89)	1.25 (0.70 – 2.23)
eGFR < 60 ml/min/m²	1.78 (1.16 – 2.75)	1.23 (0.72 – 2.11)	1.92 (1.12 – 3.31)	1.39 (0.70 – 2.74)

Table 2.14: Univariate and multivariate HR for all cause mortality and cardiovascular death for CKD stage. Values shown are HR (95% confidence interval).

Although mortality increased the further eGFR fell below 60ml/min/m², this did not prove to be independent predictors of outcome compare to eGFR >60ml/min.m² following multivariate analysis, as shown in table 2.15.

	All cause mortality		**Cardiovascular death**	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
eGFR > 60 ml/min/m²	1.0	1.0	1.0	1.0
eGFR 50-60 ml/min/m²	1.40 (0.99 – 1.94)	0.97 (0.66 – 1.44)	1.49 (0.99 – 2.20)	0.96 (0.59 – 1.57)
eGFR < 50 ml/min/m²	2.26 (1.54 – 3.30)	1.39 (0.88 – 2.17)	2.16 (1.34 – 3.49)	1.29 (0.74 – 2.24)

Table 2.15: Univariate and multivariate HR for all cause mortality and cardiovascular death per eGFR 10ml/min/1.73m² in those with eGFR < 60. Values shown are HR (95% confidence interval).

Dividing the cohort into quartiles based on eGFR revealed that, when compared to the cohort with the highest quartile, the quartile with the lowest eGFR was not independently predictive of all cause mortality (adjusted HR = 1.00 [0.68 – 1.44]), nor of cardiovascular death (adjusted HR = 0.98 [0.62 – 1.54]).

2.3.4.2 Creatinine

Dividing the cohort based on creatinine concentration also demonstrated markedly different outcome. As shown in figure 2.20, those with any degree of renal impairment had worse overall survival and a higher rate of cardiovascular death.

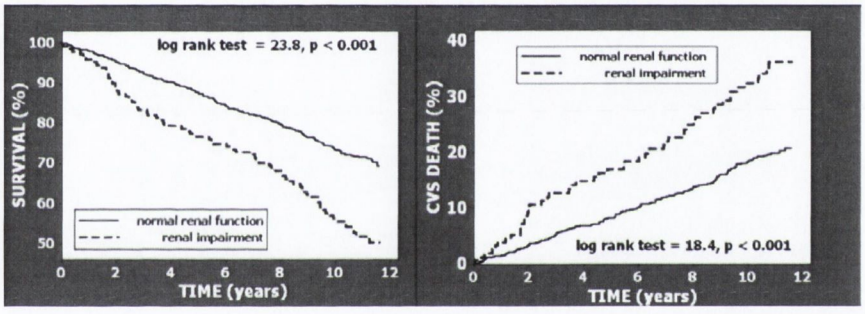


Figure 2.20 Kaplan-Meier curves of survival (left) and cardiovascular death (right) in the cohort as divided by presence of renal impairment as defined by serum creatinine.

Looking at the death coding (Table 2.16), we can see that those with renal impairment defined by serum creatinine had a similar profile of cause of death compared to those with normal renal function, although the overall death rate was higher in the former group. Specifically with regard to cardiovascular deaths, renal impairment was associated with higher crude mortality rates due to MI, HF and stroke. However the proportion of cardiovascular deaths due to MI was similar between the groups (57.6 v 55.9%), with an excess proportion of cardiovascular deaths due to HF in the renal impairment group (16.0 v 12.1% p=0.048)

Compared to those with normal renal function, the cohort with any degree of renal impairment as defined by creatinine had an unadjusted HR of 1.91 (1.47 – 2.49) for all cause mortality and 2.0 (1.45 – 2.76) for cardiovascular death. Respective adjusted HRs were 1.40 (1.03 – 1.90) and 1.46 (1.01 – 2.13).

	Normal renal function	Impaired renal function
	Creat < 106μmol/l	Creat > 106μmol/l
n	746	151
Crude mortality (%)	29.0	48.3
Cause of death (%)		
Cardiovascular	65.2	68.5
Cancer	17.9	16.3
Respiratory	5.2	6.8
Other	9.3	8.3
Crude mortality (%) due to		
Myo Infarction	10.9	18.5
Heart Failure	2.3	5.3
CVA	1.2	2.6
Other	4.6	6.6
Proportion of CVS death (%)		
Myo Infarction	57.6	55.9
Heart Failure	12.1	16.0
CVA	6.3	7.8
Other	24.3	19.9

Table 2.16: Death coding comparing those with and without renal impairment as defined by serum creatinine.

2.3.4.3 Outcome with renal function and LVSD.

The combination of LVSD and CKD carried a very poor prognosis, having much higher mortality rates than LVSD alone or CKD alone. This is illustrated in Figure 2.21. Of those individuals with both LVSD and CKD, 67.9% had died by the end of 2006, the vast majority of which (89.3%) being due to cardiovascular death. This compares to a crude mortality of

24.1% in those with neither CKD nor LVSD, 36.6% in those with CKD only, and 51.3% of those with LVSD alone.

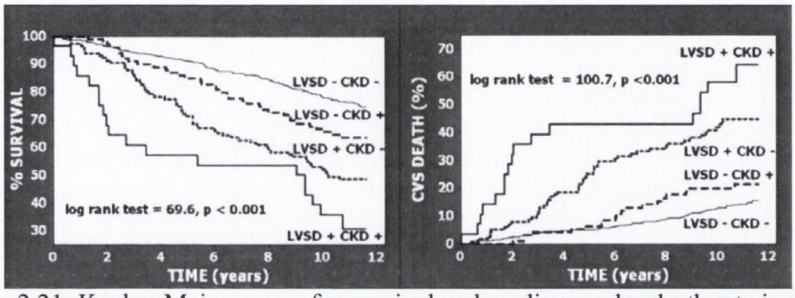


Figure 2.21: Kaplan-Meier curves for survival and cardiovascular death rate in groups divided by absence of presence of CKD and/or LVSD.

Table 2.17 details the univariate and multivariate Cox regression analysis of these groups. The presence of CKD in addition to LVSD clearly leads to poorer outcome, with almost twice as high a univariate HR for cardiovascular death compared to LVSD and normal renal function (6.77 v 3.88), for example. The incremental increase in HR with CKD is seen with both all cause mortality and cardiovascular death, and persists after multivariate analysis.

		All cause mortality		Cardiovascular death	
		Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
CKD	LVSD				
-	-	1.0	1.0	1.0	1.0
+	-	1.63 (1.13 – 2.37)	1.10 (0.73 – 1.63)	1.51 (0.91 – 2.50)	1.04 (0.61 – 1.78)
-	+	2.68 (1.97 – 3.66)	1.73 (1.06 – 2.83)	3.88 (2.70 – 5.58)	2.10 (1.15– 3.82)
+	+	4.36 (2.69 – 7.07)	1.91 (1.01 – 3.62)	6.77 (4.00– 11.50)	2.60 (1.23 – 5.48)

Table 2.17: Hazard ratios (HR) for CKD, LVSD and combination of CKD and/or LVSD for all cause mortality and cardiovascular disease. Values shown are HR (95% confidence interval).
[CKD = chronic kidney disease, LVSD = left ventricular systolic dysfunction, + = present, - = absent]

2.4 Discussion

Prognosis following acute MI can vary significantly between individuals and is influenced by factors such as age, LV function, cardiovascular risk profile and other co-morbidities. Renal function is now recognised as another measurable variable which can predict outcome and thus risk stratify patients.

Before analysing the result from this post-MI study, it's important to recognise how this cohort differed from that investigated in other studies. Virtually all of the post MI studies examining renal function and outcome recruited patients at the time of MI, whereas this post MI population were screened at least 2.5 years after their index MI. Following MI, there is a relatively rapid mortality rate in-hospital and for up to one year, after which the mortality rate falls and becomes linear. As such, the cohort examined here represents a collection of post MI "survivors", and will thus contain relatively fewer high risk patients and have a lower event rate when compared to other studies.

The relatively healthy nature of the post-MI cohort is manifest in a number of different ways. Firstly, the mean age of this cohort (61 years) is younger than most of the other referenced studies by at least two years (38,39,41,44,45,78) and even up to 6 years (82). The prevalence of hypertension in this study was 64.5%; this is comparable to that quoted in other post-MI studies (39,82) although is approximately 5-10% lower compared to other (38,45). This of course will be influenced by differing definitions of hypertension. The prevalence of DM in the majority of post MI studies varied between 20 and 30% (38,38,45,79,80,82) compared to a prevalence of 10.8% in this cohort. Finally, LVSD in this cohort was seen in 15.8%. This is certainly much lower than the quoted drug studies (38,80,119) where LVSD was an entry

criterion; most other studies do not quote LV function and as such, direct comparison is difficult.

However, the most apparent method of revealing the "healthier" nature of this cohort is to compare mortality rates. 32.7% of our cohort died during the follow up period, giving an average mortality rate of approximately 3% per year. Approximately 3% of patients studied in the Grace registry (45) or by Pitsavos et al (82) died in-hospital, with an even higher proportion dying in-hospital following thrombolysis for MI (79). 6% of patients studied in the CURE trial died in the one year follow-up and SAVE and VALIANT had a mean mortality rate of 6-8% per year (38,39,80).

Examination of the drug history of our cohort provides an historical glimpse into the development of drug therapy following post MI and LVSD. This screening visit took place in 1995, when ACE-inhibitor use in LVSD was in its infancy and before the advent of beta-blocker therapy for HF. This is reflected by a low rate of use of both therapies, with less than one in six patients with LVSD receiving a beta-blocker and only one third receiving an ACE-inhibitor. Aspirin was used in the majority of patients but only a few were taking statins. It would certainly be hoped that in 2009, almost 100% of patients following MI would be taking aspirin, a statin, a beta-blocker and ACE-inhibitor, particularly if they have LVSD.

Comparison of the genders raised some interesting results. As might be expected, women had sustained their MI almost 2.5 years later than the men and had better LV function. They were much more likely to report symptoms than men, and possibly as a result, were taking more medications.

Renal function in this cohort proved to be relatively good when compared to other post-MI studies; this would reflect the already acknowledged lesser rates of DM, hypertension and younger age, as well as the "survivor" aspect of patient selection. Only 17.1% of this post MI cohort had an eGFR < 60ml/min/1.73m^2, compared to rates of 26.6% (39), 33% (80), 33.4% (38) and 41% (42) reported elsewhere. 16.3% had elevated serum creatinine levels, compared to 24.7% reported by Hobbach et al (79) using the same diagnostic criteria. Higher rates of renal impairment were not seen in hypertensive or diabetic patients; as similarly reported elsewhere (119), renal function had no association with LV systolic function in this post MI cohort. Increased symptomatology was seen with CKD stage 3 or worse; this could be explained by increasing age and increased proportion of females or perhaps the kidney disease itself contributes to dyspnoea.

As discussed in the results section, using eGFR and creatinine cut-offs resulted in very similar rates of patients having renal impairment. However, the use of creatinine misclassified over 50 elderly women as having normal renal function when they had eGFRs less than 60ml/min/1.73m^2. CKD classification did indicate a much higher rate of CKD stage 3 or worse in women compared to men.

Approximately one third of the cohort died during the follow up period, of which a cardiovascular cause was responsible in approximately two thirds of cases. As expected, age and LV function proved to be very strong predictors of adverse outcome following MI, but gender was not even a univariate predictor. DM and hypertension were both univariate but not multivariate predictors of adverse outcome. Drug therapy revealed unusual results, at least at first glance; beta-blocker use was a univariate predictor of good outcome but ACE-

inhibitor use was associated with adverse outcome, even being a multivariate predictor of cardiovascular death. This can largely be explained by the already acknowledged prescribing habits in 1995, whereby patients with LVSD (and thus the highest risk) were more likely to be taking an ACE-inhibitor, and very unlikely to be taking a beta-blocker. In any case, this was an observational study, and there is no record of drug therapy throughout the follow period. Statin therapy at baseline was a univariate predictor of good outcome, although too few individuals were prescribed this drug to reach any firm conclusions.

eGFR proved to be a univariate predictor of both all cause mortality and cardiovascular death, and its noteworthy that increased crude mortality rates were only seen once eGFR fell below 60ml/min/1.73m^2. However, following multivariate analysis, neither eGFR nor CKD classification proved to be independently predictive of outcome. This finding is in contrast to those reported in the vast majority of post MI studied assessing eGFR and outcome (38,39,42,80) and requires some attention. As discussed, this post-MI cohort was less ill compared to other studies and as such, had a lower event rate during the follow up period; this could thereby explain our results. On the other hand, it is difficult to directly compare our study with the others given the differences between them and different time from MI; it may well be that eGFR is not an independent predictor of outcome many years after MI. It is worth noting that other post MI studies included more variables in their multivariate analysis, usually approximately ten (80,82); indeed, the VALIANT renal paper had seventy co-variates in its final model (38)!

Combining CKD status and LVSD did add incremental prognostic information. Compared to those with normal renal function and LV function, individuals with LVSD and CKD stage 3

or worse had adjusted HRs of 1.91 and 2.60 for all cause mortality and cardiovascular death respectively; this compares to respective HRs of 1.73 and 2.10 for individuals with LVSD and normal renal function.

Using serum creatinine cut-offs as definitions of renal impairment did prove to be independently predictive of both all cause mortality and cardiovascular death. However, this system is known to misclassify elderly women (as it did so here) as having normal renal function when eGFR is low; conversely, using creatinine to define renal failure tends to include more men than other systems.

It is noteworthy that renal impairment, whether classified using eGFR or creatinine was associated with an increased likelihood of dying due to HF. The number of deaths due to HF only numbered 25 in total, and as such, multivariate analysis could not be performed. However, it is easy to imagine that this is a true association; increased salt and water retention due to renal impairment could either create or exacerbate HF symptoms; in addition, increased adverse RAAS activation in more advanced HF would also lead to more renal impairment.

Renal function had a strong correlation with natriuretic peptides, thus confirming this previously reported relationship (188,216,228,229,236,237). Patients with CKD stage 3 or worse could expect to have a median BNP level twice that of those with CKD stage 1 or better. BNP proved a good method of identifying LVSD within the cohort but its main strength was with predicting prognosis. Raised BNP levels, even many years after MI, proved to be strongly predictive of death, particularly cardiovascular death.

It must be recognised that the "healthier" nature of this cohort (as detailed at the start of this discussion) will have had a significant bearing on the results. As patients were recruited several years after their index MI, it is likely that there was dilution over time of factors normally associated with poorer outcome. This may explain why variables such as diabetes mellitus and hypertension appear to be modest independent predictors of outcome; more immediately relevant to this thesis is the potential effect this had on the predictive value of renal impairment and could actually largely explain why no independent association with eGFR and outcome was established.

2.4.1 Limitations

This study had a number of limitations that should be acknowledged. More information about the index MI would have been valuable, such as type of MI (STEMI, non-STEMI), treatments (e.g. thrombolysis) and clinical situation on admission (Killip class, cardiogenic shock). Information about subsequent revascularisation (PCI, CABG) would also have been desirable. Information on urinanalysis (e.g. proteinuria or haematuria) might have been helpful in distinguishing and risk stratifying renal impairment.

This study took place in 1995. Since this time, large improvements have been made in treatment of MI and as such, prognosis is better; this includes improved drug therapy (statins, beta-blocker, ACE-inhibitor, eplerenone), increased use of PCI (including primary PCI), implantable defibrillators and cardiac resynchronisation therapy. As such, it is difficult to apply the findings of this study to the modern post MI population.

Smoking and dyslipidaemia are both recognised as factors influencing adverse cardiovascular outcome. This study was limited in that lipid analysis was not performed on this cohort and reliable smoking data was not available.

Death is of course the hardest end-point, but classification of death as cardiovascular based on information on a death certificate is not a robust method. Information on cardiovascular morbidity (further MI, hospital admission with HF etc) would have been desirable.

2.4.2 Conclusion

In this post MI cohort, the prevalence of renal impairment was approximately half that quoted in previous similar studies. Older age and female gender were strongly associated with renal impairment. Compared to other similar studies, this cohort was younger and had lower rates of LVSD, hypertension and DM. As such, subsequent mortality rates were also lower.

Renal function, when measured as eGFR, was a univariate but not multivariate predictor of all cause mortality and cardiovascular death. This could be explained by the "healthier" nature of this cohort and thus lower event rate, but it may be true that eGFR is not predictive of outcome many years after MI. CKD status did add incremental prognostic information when combined with LV function. Renal impairment, using cut-offs in serum creatinine, was independently predictive of adverse outcome, but this method is biased against women and the elderly. It appears that renal impairment following MI is associated with a higher rate of deaths due to HF. Renal function correlated strongly with natriuretic peptides. BNP in particular was a very strong predictor of adverse outcome following MI.

CHAPTER 3

POST MYOCARDIAL INFARCTION RESCREEN COHORT

3.1 Introduction

MI results in subsequent deterioration of renal function (105-108). This is primarily driven by the RAAS, as blockade of this hormonal pathway has been shown to reduce the development of renal impairment, as well as improving mortality following MI (107,108). However, decline in RF after MI may be a result of other factors; DM and hypertension are the leading causes of renal disease and will be found at high prevalence in post MI cohorts. Systemic inflammation may also play a role (111,143).

There have been extensive studies assessing outcome after MI and correlating this with a once off assessment of renal function (38,39,43,45,79,80); even mild renal impairment carries poorer prognosis compared to normal renal function. The interaction between cardiac and renal disease following MI is coming under increased scrutiny and assessing temporal change in renal function may help in understanding of cardiorenal syndromes.

A number of studies have assessed in-hospital change in renal function following MI, and noted that worsening renal function carries a poorer prognosis. An in-hospital increase in serum creatinine of even 0.3mg/dl (23.6μmol/l) after a MI carries an adjusted HR of almost two (95), and this is the case even if renal function improves (110). Chronic change in RF after MI is less well studied although some have tracked renal function for up to one month after MI (111), and some drug trials have assessed renal function for up to one year (107).

In this chapter, change in renal function over 3 years in a post MI cohort from Glasgow will be studied. Factors influencing change in renal function will be examined and the influence of

deteriorating renal function on outcome will be assessed. In addition, change in BNP levels over the same period will also be examined.

3.2 Methods

3.2.1 Patient identification

In 1998, all participants who had attended for post MI screening as detailed in section 2.2.1 in 1995 were invited to reattend. 500 subjects returned for repeat screening

3.2.2Screening visit

Screening visit was similar to that described in section 2.2.2. This incorporated a personal health questionnaire, blood pressure measurement and blood sampling. Blood samples were taken from the antecubital fossa. Analysis for blood glucose was performed. BNP levels were measured using Shionoria solid phase immunoradiometric assay from Schering CIS (France). Serum samples were frozen at time of screening. They were subsequently thawed in October 2006 and immediately analysed for creatinine concentration on an Abbott c8000 analyser using a reaction rate Jaffe method (Abbott Diagnostics, US). Serum creatinine levels have been shown to remain stable when samples are stored at very low temperatures for many years (245). Estimated glomerular filtration rate (eGFR) was then calculated for each individual using the Modified Diet in Renal Disease formula [186 x [SerumCreatinine (μmol/L) x $0.0113]^{-1.154}$ x Age $(years)^{-0.203}$ (x 0.742 if female)].

3.2.3 Definitions

The definitions for hypertension, DM, LVSD were as detailed in section 2.2.3. Renal function at baseline was defined using both eGFR and serum creatinine. Current guidelines regarding

CKD classification were used(24); for CKD stage 1 and 2, guidelines indicate that there must be evidence of kidney damage in the form of proteinuria or haematuria; urinalysis was not available to us and thus we classified patients as CKD stage 1 or 2 based solely on their calculated eGFR. All patients with eGFR < 60ml/min/1.73m^2 were classified as CKD stage 3 or worse (CKD 3+), even if they fulfilled criteria for CKD stage 4 or 5. All individuals with eGFR >90ml/min/1.73m^2 were classified as CKD stage 1 or better (CKD 1-).

Change in (Δ) renal function

Change in renal function was assessed using both creatinine concentration and eGFR. Absolute change over time was calculated by subtracting the value at baseline (1995) from the rescreen (1998) value. We investigated change in (Δ) eGFR or Δ creatinine as unknown factors with respect to outcome; both were normally distributed. We divided the groups into tertiles based on absolute Δ eGFR or Δ creatinine. Additional analysis was performed with creatinine levels; namely we classified an increase of 0.3mg/dl (equivalent to 26.5μmol/l) as worsening renal function (WRF).

Change in BNP

Absolute change in BNP over time was calculated by subtracting the value at baseline (1995) from the rescreen (1998) value.

3.2.4 Deaths

All deaths up to an including 31stDecember 2006 were collated from the Scottish Registry office. From the information on death certificates, two experienced cardiologists (Professor Henry Dargie, Dr Theresa McDonagh) coded the deaths as cardiovascular, cancer, respiratory

or other. The cardiovascular deaths were further sub classified as being due to myocardial infarction, heart failure, cerebrovascular disease or other. Where information on death certificates was missing or incomplete, the death was labelled as "uncoded".

3.2.5 Statistical analysis

The majority of continuous values were normally distributed and means were compared using an unpaired t-test or ANOVA as appropriate. Non-continuous variables were compared using a Mann-Whitney test or logarithmically transformed as appropriate. Categorical variables were compared using χ^2 test. Correlation between continuous variables was assessed using Pearson's technique. ROC analysis was used to assess the ability of Δ creatinine to identify the ΔeGFR tertile exhibiting the largest decline. Linear and logistic regression was used to identify predictors of change in renal function over time.

Kaplan-Meyer analysis was used to compare survival and cardiovascular deaths between groups, with subsequent log-rank testing. Survival between groups was then assessed using Cox regression, and hazard ratios (HR) were calculated. Univariate analysis was performed initially, followed by multivariate analysis; variables that were significantly associated with mortality from the univariate analyses ($p < 0.10$) were included in multivariate models. The specific variables included in the multivariate analysis are as highlighted in the results section. DM and gender were not univariate predictors of outcome. For assessing baseline eGFR/CKD stage and all cause mortality, co-variates included in the final analysis were age, LVEF, hypertension (yes/no) and beta-blocker use (yes/no). These co-variates were again used when assessing cardiovascular outcome, but ACE-inhibitor use (yes/no) was also included in the final model. For assessing Δ eGFR/ Δ creatinine/WRF with all cause

mortality and cardiovascular deaths, the same co-variates were used as above, but baseline eGFR or log creatinine (as appropriate) were also included in the final multivariate model.

All analysis was performed using SPSS or Minitab. A p value of less than 0.05 was considered statistically significant.

3.3Results

3.3.1 Baseline characteristics

Five hundred patients who had attended for the original screening in 1995 reattended for a further screening visit in 1998. The baseline characteristics at the original screening visit of these individuals are shown in Table 3.1.

	Baseline characteristics	
		range
N	500	-
Age (years)	61.6 ± 7.3	36.2 – 75.0
Male	74.8	-
Age at MI (years)	54.7 ± 7.1	28.4 – 65.0
BMI	27.4 ± 4.1	17.6 – 45.6
Height (cm)	166.0 ± 8.9	137.0 – 188.0
Weight (kg)	75.8 ± 14.0	39.0 ± 120.1
Systolic BP (mmHG)	139.6 ± 22.0	83.0 – 208.0
Diastolic BP (mmHG)	80.3 ± 12.7	41.0 – 130.0
Mean eGFR	73.3 ± 14.5	36.7 – 137.4
eGFR > 90 (%)	10.6	-
eGFR 60 -90 (%)	73.0	-
eGFR < 60 (%)	16.4	-
Hypertension	64.0	-
Diabetes Mellitus	8.2	-
LVSD	13.6	-
LVEF (%)	47.5 ±11.8	12.0 – 76.0
LVDD (cm)	5.3 ± 0.8	3.7 – 9.0
Angina	66.2	-
SOB	52.6	-
Medication		
Number of medications	2.35 ± 1.6	0 - 8
No medications	11.6	-
Diuretic	20.2	-
Aspirin	76.4	-
Beta-blocker	31.8	-
ACE-inhibitor	14.0	-
CCB	37.2	-
Nitrate	46.8	-
Nicorandil	0.8	-
Statin	9.2	-
Spironolactone	0.4	-
Digoxin	2.2	-
Warfarin	2.8	-

Table 3.1: Baseline characteristics at original screening of those individuals who attended for rescreening visit

The majority of patients were male (74.8%). Hypertension was common (64%) and the proportion of patients with LVSD and diabetes mellitus was 13.6% and 8.7% respectively.Only 16.4% had CKD stage 3 or worse at baseline, with the majority having an eGFR between 60 and 90 ml/min/1.73m^2. 11.6% were on no medications at all and the rate of ACE-I, beta blocker and statin therapy was low.

3.3.1.1 Rescreen non-attenders

Four hundred and twenty four patients who attended for screening in 1995 did not attend in 1998. Of these, one hundred and seventy seven (41.7%) had died whilst the remaining two hundred and forty seven were lost to follow up. The baseline characteristics of these individuals at the original screening visit are detailed in Table 3.2.

Compared to those who underwent rescreening, those individuals who died between the screening dates were significantly older (62.9 ± 6.9 v 61.6 ± 7.3 years, p = 0.05) and had much higher rates of LVSD (28.9 v 13.6%, p <0.001) and diabetes mellitus (19.8 v 8.2%, p<0.001). Hypertension (p = 0.22) and male gender (p = 0.22) did not vary between these two groups. Mean eGFR was lower in the deceased group compared to those who attended for repeat screening, but not significantly so (70.8 ± 17.9 v 73.3 ± 14.5 ml/min/m^2, p = 0.10).

The two hundred and forty seven individuals who did not attend for rescreening, and had not died in the intervening time, (that is, lost to follow up) were significantly younger than those who did attend rescreening (59.6 ±7.3 v 61.7± 7.2 years, p <0.001). Mean eGFR (p = 0.24), and rates of LVSD (p = 0.30), hypertension (p = 0.28) and diabetes mellitus (p =0.61) were all higher in those lost to follow up but not significantly so. Interestingly, those lost to follow

up were more likely to have reported symptoms, having a trend toward a higher rate of angina (72.9 v 66.2%, p = 0.07) and significantly higher rate of breathlessness (67.2 v 52.6%, p <0.001).

	All	Deceased	Lost to follow up
N	424	177	247
% male	71.4	70.0	72.5
Mean age (years)	61.0 ± 7.3	62.9 ± 6.9	59.6 ± 7.3
BMI	27.6 ± 5.0	27.6 ± 5.0	27.5 ± 4.9
Systolic BP	140.3 ± 24.9	141.1 ± 24.6	139.7 ± 25.1
Diastolic BP	79.9 ± 13.3	79.0 ± 13.4	80.6 ± 13.3
Mean eGFR	73.0 ± 16.0	70.8 ± 17.9	74.7 ± 14.3
eGFR > 90 (%)	12.1	11.0	12.9
eGFR 60 -90 (%)	68.5	64.0	71.6
eGFR < 60 (%)	19.4	25.0	15.5
HTN	65.1	72.3	60.0
DM	13.9	19.8	9.7
LVSD	18.4	28.9	10.9
LVEDD (cm)	5.5 ± 0.9	5.8 ± 1.0	5.3 ± 0.7
LVEF (%)	45.7 ± 13.0	41.4 ± 13.8	48.7 ± 11.5
Angina	73.8	75.1	72.9
SOB	70.7	75.7	67.2
Symptomatic	86.6	89.2	84.6
Medications			
Number of meds	2.7 ±1.4	2.9 ±1.5	2.5 ± 1.3
ACE-I	20.0	29.9	13.0
Statin	5.6	4.0	6.9
Aspirin	76.1	76.3	76.1
BB	28.8%	24.8	31.5
Diuretic	36.1%	45.7	29.1

Table 3.2: Characteristics at original screening visit of individuals who did not attend for repeat screening in 1998.

Overall, when comparing the baseline characteristics of the 500 patients who underwent rescreening with the 424 patients who did not, there was no significant difference in age (p = 0.17) or baseline eGFR (p = 0.79); rates of diabetes mellitus (p = 0.10), hypertension (p = 0.56), male gender (p = 0. 25) and angina (p = 0.16) did not differ. Left ventricular function was worse in those who did not reattend with a lower LVEF (p = 0.04) and a higher rate of

LVSD ($p = 0.046$). Non attenders at the rescreen were also significantly more breathless at baseline ($p < 0.001$).

3.3.2 Change in renal function

3.3.2.1 Change in eGFR

Absolute change in (Δ) eGFR between the screening visits was also normally distributed (Figure 3.1A) with a mean Δ eGFR of -1.91 ± 9.47 ml/min/1.73m², which ranged from -34.6 to +29.1ml/min/m². This corresponded to a percentage change of -1.9 ± 13.3% in eGFR, or -0.8 ± 3.6 ml/min/1.73m² annual change. ΔeGFR correlated negatively with baseline eGFR ($r = -0.307$, $p<0.001$) (Figure 3.2A). Thus, those with a higher eGFR at baseline showed a larger subsequent fall in eGFR over time; fall in eGFR per baseline CKD stage is illustrated in figure 3.2B.

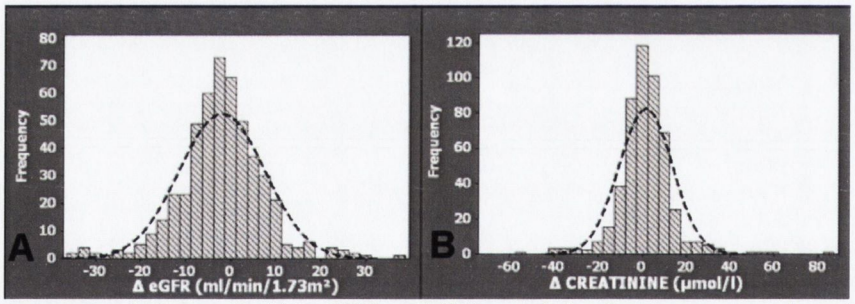


Figure 3.1: Histograms of change in (A) eGFR and (B) creatinine between screening visits in post MI cohort

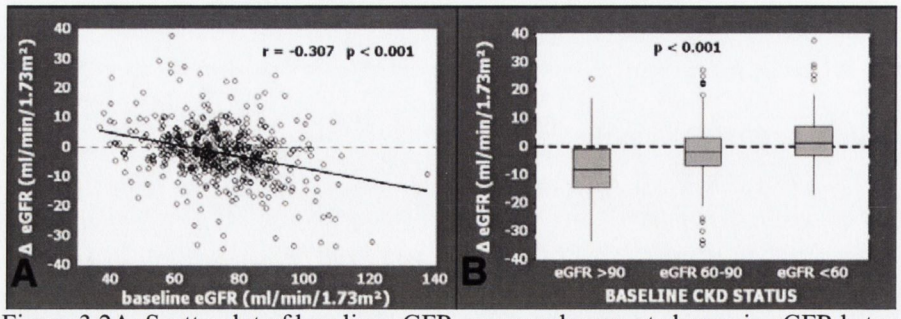


Figure 3.2A: Scatterplot of baseline eGFR versus subsequent change in eGFR between screening visits. 3.2B: Box-plot of change in eGFR as function of baseline CKD status

Using linear regression, only baseline eGFR was significantly predictive of Δ eGFR (Δ eGFR = 12.9 – 0.201 eGFR, p<0.001). Neither LVEF (p =0.62) nor age (p 0.09) had significant relationships with Δ eGFR. Although mean eGFR at baseline was higher in men, there was no difference between male and females in subsequent Δ eGFR (-1.92 ± 9.3 v -1.91 ± 9.5 ml/min/1.73m² respectively, p = 0.99); no difference was seen between the genders in ΔeGFR regardless of baseline CKD status, as illustrated in fig 3.3.

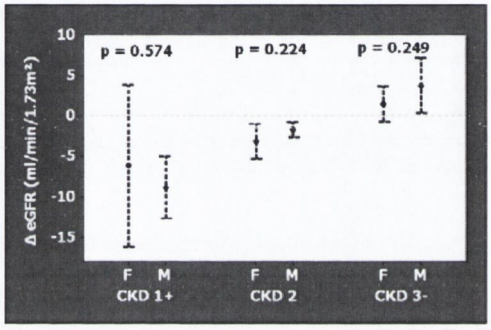


Figure 3.3: Mean ΔeGFR with 95% CI in male versus female per baseline CKD status.

Using ordinal logistic regression for ΔeGFR tertiles, having baseline eGFR < 60/ml/min/m² at baseline carried an odds ratio (OR) of 0.42 (0.27 – 0.66) of larger decline in eGFR. Neither diabetes mellitus [OR 0.89 (0.49 – 1.60)], hypertension [1.12 (0.80 – 1.56)] nor LVSD [OR 1.22 (0.76 – 1.95)] were significantly predictive of Δ eGFR. ACE-inhibitor use at baseline did not appear to influence ΔeGFR [OR 0.75 (0.47 – 1.20)], nor did diuretic use [OR 0.98 (0.65 – 1.46)]. However, beta –blocker use at baseline was significantly associated with a less severe decline in eGFR [OR 0.62 (0.44 – 0.87)].

There was no difference in mean baseline eGFR between those taking ACE-inhibitors and those not (71.1 v 73.3 ml/min/1.73m2, p = 0.28), nor between those taking a beta-blocker and those not (73.3 v 73.2 ml/min/1.73m², p = 0.68). Although no significant difference in Δ

eGFR was seen between those taking ACE-inhibitors and those not (-0.4 v -2.15 ml/min/1.73m^2, p = 0.23), those individuals taking a beta-blocker at baseline showed a significantly lower fall in eGFR over time (-0.69 v -2.45 ml/min/1.73m^2, p = 0.04).

	Δ eGFR tertile			
	Tertile 1 n=166	**Tertile 2 n = 167**	**Tertile 3 n = 167**	**p value**
Δ eGFR- mean (ml/min/1.73m^2)	-11.5	-1.9	+7.6	
Δ eGFR- range (ml/min/1.73m^2)	-34.6 to -4.9	-4.9 to +1.2	+1.2 to +37.5	
Age [years]	61.6 ± 7.6	62.5 ± 7.0	60.9 ± 7.3	0.120
Male [%]	77.1	73.7	73.7	0.704
Age at MI [years]	54.3 ± 6.9	55.6 ± 7.1	54.1 ± 7.2	0.098
Hypertension [%]	64.4	66.5	61.1	0.584
Diabetes mellitus [%]	7.8	7.8	9.0	0.903
BMI [kg/m^2]	26.9 ± 4.2	27.4 ± 4.1	27.9 ± 4.0	0.128
LVSD [%]	15.1	13.8	12.0	0.712
LV ejection fraction	47.1 ± 11.8	47.8 ± 12.0	47.8 ± 11.7	0.842
Baseline median creatinine* [μmol/l]	86.4	93.7	94.9	**<0.001**
Baseline eGFR (ml/min/1.73m^2)	78.8 ± 14.5	71.7 ± 13.7	69.6 ± 13.6	**<0.001**
Baseline eGFR > 90 (%)	19.3	7.2	6.0	}
Baseline eGFR 60 -90 (%)	74.1	73.6	77.3	} **<0.001**
Baseline eGFR < 60 (%)	6.6	19.2	22.7	}
Systolic BP [mmHG]	141.1 ± 24.0	140.8 ± 19.5	137.0 ± 22.3	0.170
Diastolic BP[mmHG]	81.0 ± 14.0	80.0 ± 11.1	79.7 ± 13.0	0.634
Self reported symptoms				
SOB [%]	56.6	47.9	53.3	0.274
Angina [%]	70.5	62.9	65.2	0.325
Symptomatic [%]	79.5	71.3	77.8	0.173
Medication[a]				
Aspirin [%]	74.1	79.1	76.0	0.564
Beta blocker [%]	27.1	27.5	40.7	**0.010**
ACE-I [%]	15.1	7.8	19.1	**0.010**
Statin [%]	8.4	9.0	10.2	0.853
Diuretic [%]	20.5	19.2	21.0	0.914

Table 3.3: baseline characteristics of cohort as a function of ΔeGFR tertile

The cohort was divided into tertiles based on ΔeGFR over time. Baseline characteristics as a function of Δ eGFR tertiles is shown in table 3.3. As demonstrated, the cohorts were very similar at baseline with no difference in mean age, gender mix of age from MI. It is also noteworthy that the rate of hypertension, diabetes mellitus and LV systolic function did not differ between the groups. As already noted, the tertile with the largest subsequent fall in

eGFR actually had better renal function at baseline; this tertile also had lower rate of beta-blocker and ACE-inhibitor use at baseline.

3.3.2.2 Change in creatinine and worsening renal function (WRF)

Absolute change in (Δ) creatinine was normally distributed (Figure 3.1B) with a mean Δ creatinine of +1.65 ± 12.1 μmol/l. This corresponded to a percentage change of +2.3 ± 12.6% in creatinine, or +0.7 ± 4.7 μmol/l annual change.Δ creatinine correlated negatively with baseline log creatinine ($r = -0.236$, $p < 0.001$). Not surprisingly, there was a close association between Δ creatinine and Δ eGFR; they had a strong negative correlation ($r = -0.913$, $p < 0.001$). Taking the largest fall in eGFR (i.e. tertile 1) as the gold standard test for deteriorating renal function, we can see that Δ creatinine proved very good at identifying these patients (figure 3.4)

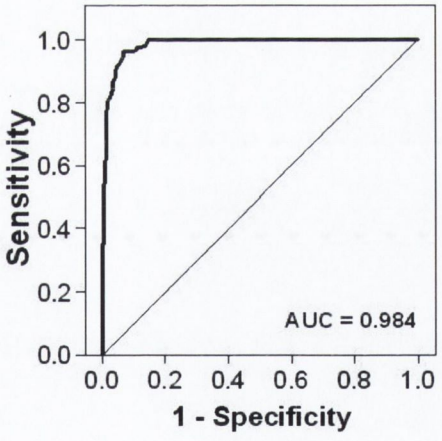


Figure 3.4: ROC curve for ability of Δ creatinine to identify the tertile with the largest fall in eGFR

Only seventeen (3.4%) individuals exhibited an increase in creatinine of >0.3mg/dl (26.5 μmol/l), thus fulfilling criteria for WRF. The characteristics of these individuals at the original screening visit are detailed in table 3.4. Those who exhibited WRF were older, more

likely to be female and more symptomatic than those who did not exhibit WRF. LVSD had an OR of 2.8 (0.93 – 8.47, p= 0.087) for the development of WRF.

	WRF	Not WRF	p value
N	17	483	
Age	66.7 ±5.6	61.5 ± 7.3	0.002
Male	52.9	75.6	0.035
LVEF	42.8 ± 15.3	47.7 ± 11.6	0.180
LVSD	29.4	13.0	0.053
LVEDD	5.7 ± 0.9	5.3 ± 0.8	0.157
HTN	76.5	63.6	0.276
DM	5.9	8.3	0.723
eGFR at baseline	73.5 ± 14.3	68.2 ±16.9	0.220
Angina	82.4	65.6	0.030
SOB	76.5	51.8	0.045

Table 3.4. Characteristics at baseline screening of those individuals who fulfilled criteria for worsening renal function (WRF) versus those who did not.

3.3.3Brain natriuretic peptide

Four hundred and eighty one patients had BNP levels measured in both the 1995 and 1998 screening. Baseline median (IQ range) BNP was 33.0 (51.8)pg/ml. Absolute change (Δ) in BNP between the screening visits was normally distributed with a mean change of +25.3 ±100.4pg/ml, and ranged from -233 to +1151pg/ml. (see figure 3.5A). There was no significant relationship between baseline BNP and subsequent Δ BNP; baseline log BNP did not correlate with Δ BNP (r = 0.035, p = 0.48). As illustrated in figure 3.5B, there was no significant difference in mean Δ BNP between baseline BNP quartiles although it appears that as baseline BNP quartile increased, the range of Δ BNP increased also.

Δ BNP did not vary according to baseline renal function. There was no correlation between baseline eGFR and Δ BNP (r = -0.0 70, p = 0.123) and the mean Δ BNP did not differ between those with eGFR > 60 ml/min/1.73m² of those with eGFR below this (+ 23.9 ± 91.0 v +32.0 ± 140pg/ml, p =0.609).

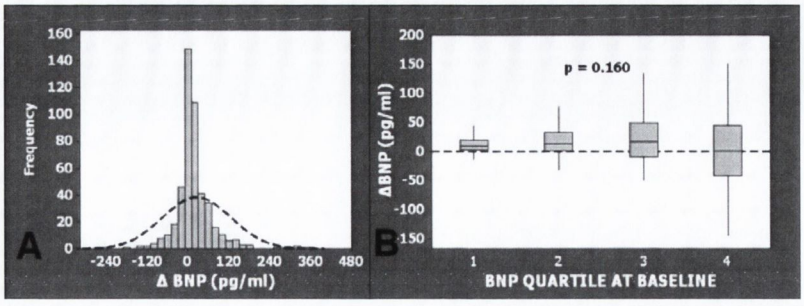


Figure 3.5. A Histogram of absolute change in BNP between screening visits. B Box-plot of change in BNP as function of baseline BNP quartile (quartile 1 = lowest)

However, elevated BNP levels at baseline were associated with a greater subsequent fall in eGFR; log BNP correlated with Δ eGFR($r = -0.139$, $p = 0.002$). Figure 3.6 illustrates mean Δ eGFR as a function of baseline BNP tertile (tertile 1 is lowest). Using linear regression, log BNP at baseline was predictive of Δ eGFR (Δ eGFR = 2.43 – 2.88 log BNP, $p = 0.002$).

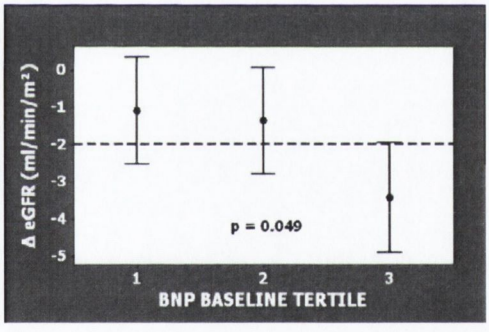


Figure 3.6: Interval plot showing mean ΔBNP, with 95% CI as a function of baseline BNP tertile (tertile 1 is lowest)

3.4.4 Outcome

All deaths were recorded up to and including the 31st December 2006. Mean follow- up was 8.3 ± 0.6 years. Of the five hundred study participants, one hundred and twenty three (24.6%) had died by the end of this period. As demonstrated in figure 3.7, the rate of death was linear throughout the follow up period.

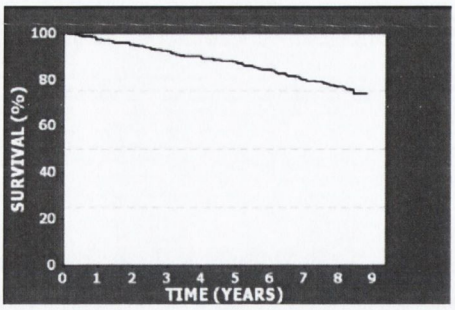


Figure 3.7 Kaplan-Meier curve of survival of post MI rescreen cohort during follow up period

The deaths were coded thus:

- Cardiovascular deaths 85 (69.1% of all deaths)
- Cancer deaths 17 (13.8%)
- Respiratory deaths 6 (4.8%)
- Other 11 (8.1%)
- Uncoded 6 (4.9%)

Of the cardiovascular deaths, forty four (51.7%) were attributed to a myocardial infarction, eleven (12.9%) to heart failure, eight (9.4%) to cerebrovascular disease and the remaining twenty two (25.9%) were due to another type of cardiovascular death.

Table 3.5 illustrates univariate HRs for all cause mortality and cardiovascular death following Cox regression analysis. LVSD proved to be a strong univariate predictor of outcome. Diabetes mellitus did not exhibit statistically significant univariate HRs but hypertension did show a trend toward significance with p values for both all cause mortality and cardiovascular death falling between 0.05 and 0.1. Angina was not a univariate predictor of outcome; however, breathlessness did predict cardiovascular death with a univariate HR of 2.15. Statin treatment at the original screening had no association with outcome, and although ACE-

inhibitor use did not predict all cause mortality, it did carry a statistically significant univariate HR (1.69) for adverse outcome in terms of cardiovascular death. Beta- blocker use at the original screening was associated with a better outcome with both all cause mortality and cardiovascular death

	All cause mortality			Cardiovascular death		
	HR	95% CI	p value	HR	95% HR	p value
Male	0.93	0.62 – 1.40	0.718	1.24	0.73 – 2.08	0.427
Age*	1.08	1.05 – 1.12	<0.001	1.08	1.04 – 1.12	<0.001
LVEF*	0.97	0.96 – 0.99	0.001	0.96	0.94 – 0.98	<0.001
LVSD	2.48	1.63 – 3.79	<0.001	3.60	2.19 – 5.88	<0.001
LVEDD*	1.69	1.24 – 2.30	0.001	2.17	1.53 – 3.08	<0.001
SOB	1.61	1.12 – 2.30	0.10	2.15	1.37 – 3.42	0.001
Angina	1.14	0.78 – 1.66	0.496	1.47	0.90 – 2.39	0.124
HTN	1.41	0.97 – 2.08	0.074	1.58	0.97 – 2.53	0.065
DM	1.11	0.60 – 2.05	0.751	1.38	0.69 – 2.75	0.362
ACE-I	1.32	0.83 – 2.10	0.238	1.69	1.0 – 2.94	0.050
BB	0.56	0.34 – 0.86	0.007	0.51	0.30 – 0.88	0.014
Statin	0.55	0.26 – 1.18	0.125	0.71	0.31 – 1.64	0.424

Table 3.5: Univariate hazard ratios for all cause mortality and cardiovascular death in post MI rescreen cohort (* continuous variable)

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All variables with univariate HR with p values <0.1 were included in the final model for multivariate analysis. The results of this are shown in table 3.6. Hypertension, beta-blocker use and ACE-inhibitor use were not independent predictors of all cause mortality, or of cardiovascular death. LVSD was a strong independent predictor of outcome, carrying a three fold increased risk of cardiovascular death. Reporting breathlessness at screening carried an adjusted HR of 2.48 for cardiovascular death.

	All cause mortality			Cardiovascular death		
	HR	95% CI	p value	HR	95% CI	p value
Age*	1.08	1.05 – 1.12	<0.001	1.08	1.04 – 1.13	<0.001
LVSD	2.17	1.40 – 3.34	<0.001	3.00	1.80 – 5.00	<0.001
SOB	1.76	1.19 – 2.62	0.005	2.48	1.47 – 4.16	0.001
HTN	1.51	0.98 – 2.32	0.062	1.73	0.99 – 2.99	0.055
ACE-I	-	-	-	1.63	0.93 – 2.87	0.90
BB	0.66	0.41 – 1.06	0.082	0.63	0.34 – 1.19	0.152

Table 3.6 Multivariate hazard ratios for all cause mortality and cardiovascular death in post MI rescreen cohort (* continuous variable).

3.3.5 Natriuretic peptides and outcome

BNP levels at baseline screening proved strongly predictive of outcome. LogBNP had an unadjusted HR of 2.72 (1.80 – 4.10) for all cause mortality and 3.87 (2.35 – 6.40) for cardiovascular death; respective adjusted HRs were 1.83 (1.11 – 3.02) and 2.41 (1.29 – 4.50). Fig 3.8A and 3.8B reveal Kaplan-Meier curves for all cause mortality and cardiovascular deaths for the cohort as a function of baseline BNP quartile; a clear step wise increase in adverse outcome is seen as baseline BNP levels increased. Compared to the quartile 1 (lowest BNP), quartiles 2, 3 and 4 had unadjusted HRs for all cause mortality of 1.60 (0.85 – 3.02), 2.41 (1.33 – 4.36) and 3.15 (1.78 – 5.58) respectively.

Δ BNP, when assessed as a continuous variable, was a univariate predictor of adverse outcome with unadjusted HR of 1.002 (1.001-1.003, $p = 0.004$) for all cause mortality and 1.002 (1.001 – 1.003, $p < 0.001$) for cardiovascular death. Following multivariate analysis (including logBNP at baseline as a covariate), ΔBNP remained an independent predictor of outcome with adjusted HR for all cause mortality and cardiovascular death of 1.002 (1.000 – 1.003, $p = 0.01$) and 1.002 (1.001 – 1.004, $p < 0.001$) respectively.

When the cohort was divided into quartiles based on Δ BNP, the quartile showing the largest increase in BNP (quartile 4) did have the highest rate of adverse outcomes, although the other three quartiles did not differ greatly; this is illustrated in fig 3.8C and 3.8D. HR for all cause mortality and cardiovascular death are shown in Table 3.7, and illustrates that ΔBNP quartiles did not have a significant association with long term outcome.

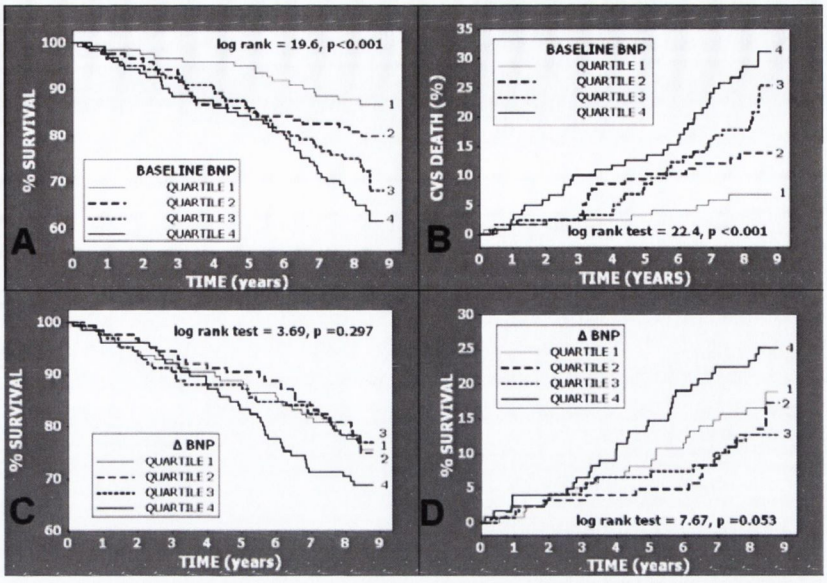

Fig 3.8: Kaplan-Meier curves of: BNP quartiles at baseline and all cause mortality (A) and cardiovascular death (B) and; Δ BNP quartiles and all cause mortality (C) and cardiovascular death (D)

		All cause mortality		Cardiovascular death	
Δ BNP	**Mean ΔBNP (pg/ml)**	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
Quartile 1	-36.3 ± 38.4	1.0	1.0	1.0	1.0
Quartile 2	+3.1 ± 3.8	0.97 (0.58 – 1.62)	1.03 (0.58 – 1.82)	0.83 (0.44 – 1.56)	1.21 (0.58 – 2.56)
Quartile 3	+19.5 ± 6.5	0.97 (0.58 – 1.62)	1.00 (0.59 – 1.75)	0.71 (0.34 – 1.39)	0.90 (0.41 – 1.99)
Quartile 4	+114.2 ± 162.9	1.41 (0.87 – 2.28)	1.17 (0.68 – 2.00)	1.52 (0.87 – 3.66)	1.74 (0.93 – 3.30)

Table 3.7: Univariate and multivariate hazard ratios for all cause mortality and cardiovascular death per ΔBNP quartile

3.3.6 Renal function and outcome

3.3.6.1 Baseline renal function

Lower renal function at baseline was associated with poorer outcome. Baseline CKD stage 1 or better and stage 2 had similar long term outcomes with crude mortality rates of 20.4% and 23.3% respectively; this compares to a crude mortality rate of 35.8% for those who had CKD stage 3 or worse at baseline. Fig 3.9A and 3.9B shows outcome curves when the cohort was

categorized based on whether baseline eGFR was greater/less than 60ml/min/1.73m^2, i.e. CKD stage 3 or worse compared to those with better renal function.

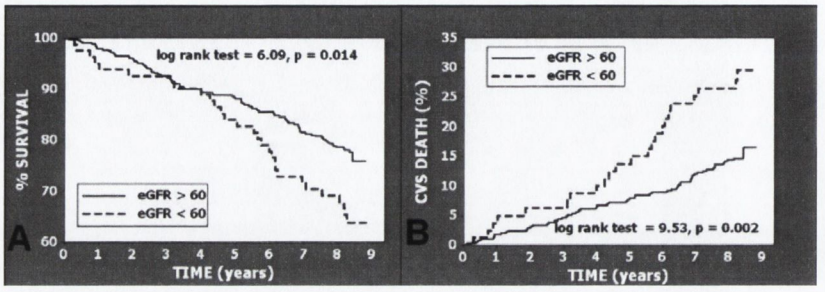

Fig 3.9: Kaplan-Meier curves of survival (A) and cardiovascular death (B) as a function of baseline eGFR greater or less than 60ml/min/1.73m^2

Compared to those with eGFR >60 ml/min/1.73m^2 at baseline, CKD stage 3 or worse was predictive of all cause mortality with an unadjusted HR of 1.68 (1.11 – 2.54, p = 0.014); However, following multivariate analysis it proved not to be an independent predictor of adverse outcome with an adjusted HR of 0.99 (0.59 – 1.65, p = 0.95). A similar picture was seen with regard to cardiovascular death with unadjusted and adjusted HRs of 2.10 (1.30 – 3.79, p = 0.002) and 1.17 (0.63 – 2.16, p = 0.62) respectively.

Assessed as a continuous variable, baseline eGFR was a univariate predictor of all cause mortality [HR 0.98 (0.97- 1.00), p = 0.019] and of cardiovascular death [HR 0.98 (0.97 – 1.00), p = 0.010]. However, following multivariate analysis, eGFR was no longer an independent predictor of outcome with adjusted HRs for all cause mortality and cardiovascular death of 1.04 (0.99 – 1.02), p = 0.63 and 1.00 (0.98 – 1.02), p = 0.96 respectively.

3.3.6.2 Change in renal function

ΔeGFR

A decline in renal function between the screening visits was associated with poorer outcome. Assessed as a continuous variable, Δ eGFR was predictive of all cause mortality with an unadjusted HR of 0.981 (0.963 – 1.000, p = 0.049); this increased to 0.970 (0.951 – 0.990, p =0.004) when adjusted for baseline eGFR. Following additional adjustment for LVEF, age, hypertension and beta-blocker use, Δ eGFR proved not to be an independent predictor of all cause mortality with a multivariate HR of 0.986 (0.965 – 1.007, p = 0.19).In terms of cardiovascular death, Δ eGFR carried an unadjusted HR of 0.976 (0.954 – 0.999, p = 0.037), which became 0.962 (0.939 – 0.986, p = 0.002) when adjusted for baseline eGFR. However, following multivariate analysis, Δ eGFR was an independent predictor of cardiovascular death with an adjusted HR of 0.973 (0.948 – 0.998, p =0.04).

All cause survival and cumulative cardiovascular death rate for the Δ eGFR tertiles over the 9 years of follow up are illustrated in fig 3.10. A clear pattern is seen, with a step-wise increase in adverse events as Δ eGFR increases, i.e. a larger decline in eGFR.

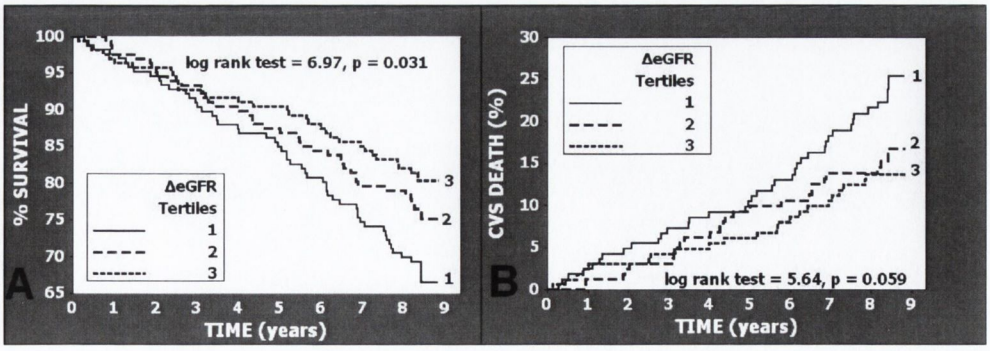

Figure 3.10: Kaplan-Meier curves of survival (A) and cardiovascular death (B) as a function of ΔeGFR tertiles.

Figure 3.11 demonstrates crude mortality rate when the cohort was divided as a function of baseline CKD status, and further divided as per Δ eGFR tertile. It reveals that Δ eGFR tertile was associated with poor outcome in those with CKD stage 2 at baseline and in those with CKD stage 3 or worse. This effect was not apparent in the small group with CKD stage 1 or better at baseline. The cumulative effect of poor baseline renal function and larger fall in eGFR in also illustrated in fig 3.11; those with CKD stage 3 or worse at baseline and in the worst Δ eGFR tertile had by far the worst outcome, with a crude mortality over the 9 years follow up of almost 75%.

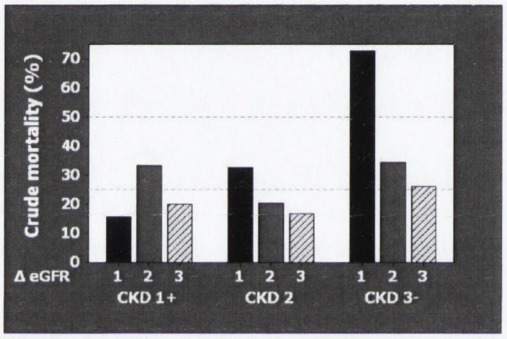

Figure 3.11: Barchart of crude mortality per baseline CKD status and subsequent ΔeGFR tertile

Death coding per ΔeGFR tertile is shown in Table 3.8. The tertiles had comparable proportion of deaths due to cardiovascular cause. The tertile with the biggest fall i.e. tertile 1 had a higher rate cancer deaths compared to the other tertiles. The proportion of cardiovascular deaths attributable to MI was lower in tertile 1, with a much higher proportion being attributed to "other ".

	Tertile 1	Tertile 2	Tertile 3
n	166	167	167
Crude mortality (%)	31.9	24.0	19.2
Cause of death (%)			
Cardiovascular	71.7	70.0	71.9
Cancer	20.8	10.0	6.3
Respiratory	1.9	10.0	3.1
Other	7.5	10.0	15.6
Crude mortality(%) due to			
Myo Infarction	9.0	9.0	9.0
Heart Failure	3.0	3.0	1.8
CVA	2.4	3.0	0.0
Other	8.4	1.8	3.0
Cause of CVS death (%)			
Myo Infarction	39.5	53.6	65.2
Heart Failure	13.2	17.9	13.0
CVA	10.5	17.9	0.0
Other	36.8	10.7	21.7

Table 3.8: Death coding per ΔeGFR tertile.

Unadjusted and adjusted HRs for Δ eGFR tertiles is detailed in Table 3.9; a larger fall in eGFR over time is independently predictive of both all cause mortality, and specifically of cardiovascular death.

	All cause mortality		Cardiovascular mortality	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Δ eGFR				
Tertile1	1.77 (1.14 - 2.72)	1.66 (1.01 – 2.71)	1.79 (1.06 – 3.04)	1.84 (1.01 – 3.36)
Tertile 2	1.27 (0.80 - 2.02)	0.93 (0.55 – 1.58)	1.16 (0.65 – 2.06)	0.85 0.43 – 1.68)
Tertile3	1.0	1.0	1.0	1.0
Δ Creatinine				
Tertile1	1.70 (1.11 – 2.61	1.48 (0.92 -2.39)	1.65 (1.0 – 2.73)	1.50 (0.85 – 2.64)
Tertile 2	1.05 (0.66 – 1.68)	0.88 (0.51 – 1.50)	0.79 (0.44 – 1.42)	0.66 (0.33 – 1.33)
Tertile3	1.0	1.0	1.0	1.0

Table 3.9: Univariate and multivariate hazard ratios for all cause mortality and cardiovascular death per ΔeGFR tertile and ΔCreatinine tertile

Almost exactly one third of the cohort (167 patients) exhibited a fall in eGFR of >5ml/min/1.73m² (117), with the remaining patients exhibiting stable renal function (i.e. a rise in eGFR or a fall in eGFR of < 5ml/min/1.73m²). Figure 3.12 demonstrates long term outcome of the cohort when divided in this manner.

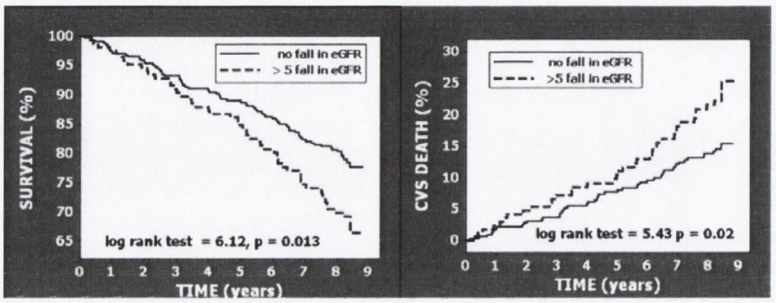

Figure 3.12: Kaplan-Meier curves of survival (left) and cardiovascular death (right) comparing stable renal function with a fall in eGFR of > 5ml/min/1.73m²

Those with a fall >5ml/min/1.73m² had poorer outcome compared to the remaining group with unadjusted HRs of 1.56 (1.09 – 2.22) and 1.66 (1.08 – 2.56) for all cause mortality and cardiovascular death respectively. Following multivariate analysis, corresponding adjusted HRs were 1.76 (1.21 – 2.67) and 2.13 (1.30 – 3.50).

Δ creatinine

Δ creatinine, assessed as a continuous variable, was a univariate predictor of both all cause mortality [HR= 1.019 (1.006 – 1.032), p = 0.004] and cardiovascular death [HR = 1.024 (1.009 – 1.038), p = 0.001]. Following multivariate analysis, Δ creatinine was no longer predictive of all cause mortality [adjusted HR = 1.010 (0.997 – 1.023), p = 0.13] but remained an independent predictor of cardiovascular death [adjusted HR = 1.016 (1.002 – 1.030), p = 0.028].

The cohort was divided into tertiles based on Δ creatinine. Figure 3.13 illustrates Kaplan-Meier curves for survival and cumulative cardiovascular death as a function of Δ creatinine tertiles.

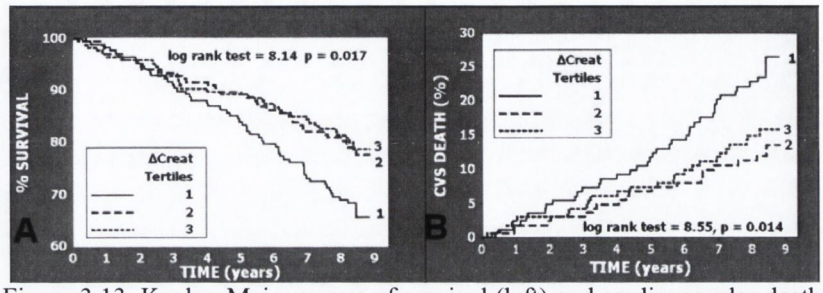

Figure 3.13: Kaplan-Meier curves of survival (left) and cardiovascular death (right) as a function of Δcreat tertiles.

The tertile with the largest rise in creatinine (tertile 1) did have the worst outcome. Tertiles 2 and 3 had similar outcome, with tertile 3 actually having a higher rate of cardiovascular death. As shown in Table 3.9, Δ creatinine tertiles were univariate predictors of outcome; however, following multivariate analysis Δ creatinine tertiles did not independently predict either all cause mortality or cardiovascular death.

Worsening renal function (WRF)

Figure 3.14 illustrates outcome over the 9 years follow up period, comparing those individuals who fulfilled the criteria of worsening renal function (WRF) with the remainder of the cohort.

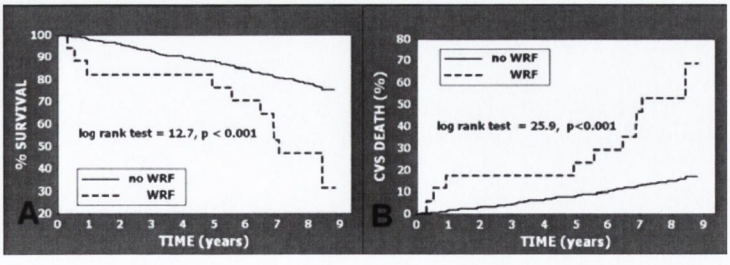

Figure 3.14: Kaplan-Meier curves of survival (left) and cardiovascular death (right) of WRF versus no WRF

Death coding for WRF versus no WRF is shown in table 3.10. All deaths in the WRF group were cardiovascular deaths, and crude mortality rates for all causes of CVS death were higher in the WRF group. Proportionately, the main excess of deaths were in "other" cardiovascular deaths.

	WRF	No WRF
n	17	483
Crude mortality (%)	58.8	23.8
Cause of death (%)		
Cardiovascular	100	68.7
Cancer	0	14.8
Respiratory	0	5.2
Other	0	11.3
Crude mortality (&) due to		
Myo Infarction	17.6	8.7
Heart Failure	5.9	2.5
CVA	5.9	1.7
Other	29.4	3.5
Proportion of CVS death (%)		
Myo Infarction	30.0	53.2
Heart Failure	10.0	15.2
CVA	10.0	10.1
Other	50.0	21.5

Table 3.10: Death coding, WRF versus no WRF.

WRF carried a univariate HR of 3.05 (1.60 – 5.82) for all cause mortality and 4.74 (2.45 – 9.18) for cardiovascular death. Following multivariate analysis, the respective adjusted HRs were 1.93 (0.93 – 3.90, p = 0.066) and 3.22 (1.54 – 6.73, p =0.022).

3.3.7 Baseline BNP and Δ eGFR

Baseline BNP and subsequent Δ eGFR are thus both independent predictors of outcome. In order to try to further risk stratify our cohort, the group was divided based on whether baseline BNP was greater than of less than the median, and then further divided based on

whether Δ eGFR was greater than or less than the median. The characteristics of these groups are detailed in figure 3.11.

	baseline BNP > median		baseline BNP < median	
	ΔeGFR > median	ΔeGFR < median	ΔeGFR > median	ΔeGFR < median
n	136	104	104	137
age (years)	62.8 ± 7.0	63.2 ± 6.7	60.3 ± 7.5	66.3 ± 7.4
Male (%)	72.2	62.5	83.6	79.5
LVEF (%)	44.7 ± 13.5	46.3 ± 13.7	50.7 ± 8.3	48.5 ± 9.9
DM	8.8	8.7	6.7	7.3
HTN	67.6	65.4	61.5	59.1
LVSD	24.2	18.3	2.9	8.1
Angina	72.1	69.2	66.4	57.7
SOB	55.2	58.7	50.0	47.5
Baseline BNP	71.2	66.8	14.6	18.0
Baseline eGFR	74.3 ± 14.4	68.4 ± 14.6	79.2 ± 14.7	72.2 ± 13.1

Table 3.11: Baseline characteristics of post MI rescreen cohort divided based on baseline BNP and subsequent ΔeGFR.

Long term outcome of the cohort when divided in this way is shown in Figure 3.15 As expected, those with a higher BNP at baseline had a poorer outcome, but subsequent ΔeGFR provided incremental prognostic information.

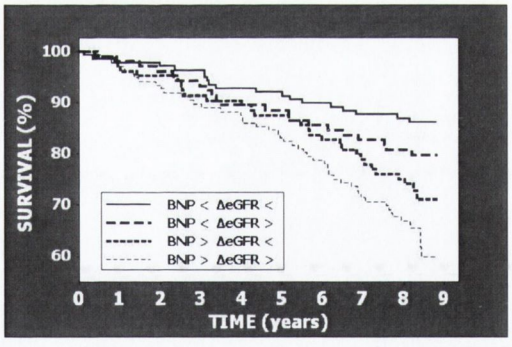

Figure 3.15: Kaplan-Meier curve of survival post MI rescreen cohort divided based on baseline BNP and subsequent ΔeGFR.

This proved predictive of all cause mortality and cardiovascular death, independent of age, hypertension, LV function and baseline renal function (table 3.12).

	baseline BNP > median		baseline BNP < median	
	ΔeGFR > median	ΔeGFR < median	ΔeGFR > median	ΔeGFR < median
Crude mortality (%)	36.7	27.9	20.2	13.9
Unadjusted HR	2.96 (1.75 – 5.02)	2.15 (1.20- 3.83)	1.50 (0.80 – 2.79)	1.0
Adjusted HR*	2.25 (1.29 – 4.10)	1.82 (0.94 - 3.49)	1.65 (0.83 - 3.30)	1.0
CVS death rate (%)	26.5	22.1	11.5	8.8
Unadjusted HR	3.39 (1.76 – 6.59)	2.71 (1.35 - 5.47)	1.35 (0.61 – 3.01)	1.0
Adjusted HR*	2.58 (1.20 – 5.54)	2.35 (1.05 – 5.25)	1.53 (0.62 - 3.80)	1.0

Table 3.12: Univaraite and multivariate hazard ratios for al cause mortality and cardiovascular death for post MI rescreen cohort divided based on baseline BNP and subsequent ΔeGFR. (*Adjusted for age, LVEF, baseline eGFR and HTN)

3.4 Discussion

MI leads to subsequent decline in RF, largely driven by the RAAS (106-108). Most studies assessing this change in renal function have incorporated patients enrolled immediately at the time of MI. It has to be acknowledged that this cohort was screened many years after their MI and as already detailed in section 2.4 of this thesis, already represented a relatively well group of post MI survivors. As such, it appears that renal function was relatively stable in this study group. eGFR fell by a mean of 1.91 ± 4.7ml/min/1.73m² between the screenings, giving an approximate annual fall in eGFR of 0.8ml/min/1.73m². Immediately following MI, renal function has been reported to fall by a mean of 2.2ml/min/1.73m² per year, compared to a 0.5ml/min/1.73m² fall in non-MI controls (106). Thus, eGFR in our cohort fell quicker than that of the general population but not as quickly as in the immediate post MI period. Only 3.4% of our cohort exhibited a rise in creatinine that fulfilled the criteria of WRF; we can compare this to a 12% rate of WRF quoted by Jose et al using similar criteria (95), and to 9.6% quoted by Goldberg at al (109), who actually used a larger rise in creatinine (>0.5mg/dL) as cut-off for WRF.

The relatively stable nature of renal function in our study can be explained by a number of issues. Firstly, our cohort reflects a clinically stable group of patients, compared to acutely unwell recruits in these other studied (95,109,110) where wide fluctuations in renal function might be expected due to physiological and pharmacological stressors. This would be more pronounced in-hospital but could be expected to extend up to a year post MI as adverse activation of the RAAS develops. As well as being clinically stable, as discussed in section 2.4, this cohort also represents a healthier group of post MI patients with a younger mean age, and lower rates of DM, hypertension and subsequent mortality.

It might have been expected that hypertension, DM and LVSD would be associated with a more marked fall in renal function over time given that these factors are known to predict the development of renal impairment in the general population (27,53). This proved not be the case and change in renal function was also independent of other factors such as gender or age. Only baseline renal function correlated with subsequent change in renal function; however, the finding that the largest fall in renal function was seen in those individuals with better renal function at baseline should not be over interpreted. This observation is probably largely explained by the phenomenon of regression to the mean, due to intra-individual variability and measurement error in creatinine assessment.

ACE-inhibitor therapy is known to protect renal function following MI (107,108) and forms the mainstay of drug therapy for slowing renal decline in CKD (25); in this study, there was no evidence of renal protection with ACE-inhibitor use. However, beta-blocker use was associated with less severe decline in renal function over time although these findings are

limited by their observational non-randomised nature. Furthermore, this only reflects drug therapy at the time of screening and there is no record of subsequent drug therapy.

In this study, chronic change in renal function over time after MI proved predictive of adverse outcome, and particularly with cardiovascular death. The tertile with the largest fall in eGFR had adjusted increased risk of 66% for all cause mortality and 84% of cardiovascular death, compared to the best tertile. This was independent of LV function, age, hypertension, DM and baseline renal function. Those individuals who fulfilled the criteria for WRF had a much worse outcome; although the HRs for this were somewhat impressive, they did only apply to a very small proportion of individuals.

Although the largest fall in renal function was seen in patients with better renal function at baseline, it is important to clarify that overall, lower eGFR at baseline was still associated with poorer outcome with CKD stage 3 or worse having univariate HRs of 1.68 (1.11 - 2.54) and 2.10 (1.30 - 3.79) for all cause mortality and cardiovascular death respectively. However, as was seen in chapter 2, renal impairment was not independently predictive of outcome after multivariate analysis. It was noted in chapter 2 that renal impairment was associated with an increased chance of subsequent of death from HF. No such association with seen with change in renal function, with increased mortality seen in all modes of death, and all modes of cardiovascular death.

Renal function was seen to improve over time in a number of patients, with some individuals having marked an increase in eGFR. The characteristics of these patients can be viewed as tertile 3 in table 3.3, and they exhibited a mean increase in eGFR of 7.6 ml/min/1.73m

between screening visits. Whilst regression to the mean could partially explain this, the larger changes in eGFR may have been due to cessation of nephrotoxic drugs, acute illness at the time of the first screening or loss of muscle bulk between the screening visits (and thus fall in creatinine). Regardless of the cause of this improvement in renal function, these individuals had the best prognosis.

Selection bias must be discussed as this could clearly influence interpretation of the results. Four hundred and twenty four patients failed to attend for the second screening visit, one hundred and seventy seven because of death. The characteristics of the non-attenders are detailed in table 3.2 and are included for comparative purposes. Compared to the 500 individuals who were incorporated into this study, those who died between screening visits were older, had worse renal function and worse LV function. In contrast, the 247 individuals who were lost to follow up, compared to the study participants, were younger, and had better renal function and LV function. It could be argued that the deceased and the lost to follow up groups countered each other in terms of effect on the study, perhaps reducing selection bias to a degree; overall, non-attenders (n = 424) and attenders (n = 500) did not differ in terms of age, eGFR, LV function, gender, hypertension or DM. Those individuals lost to follow up did have relatively higher rates of reported symptoms at the baseline screening and poor exercise tolerance may explain their non attendance at the second screening visit.

The temporal relationship between renal function and BNP was of interest. Raised BNP at baseline was predictive of larger subsequent fall in eGFR; BNP is a surrogate marker of LV stress, and as such might correlate with severity of cardiac disease and thus, RAAS activity.

This might therefore act as the causal link between elevated BNP and declining renal function.

No real relationship was seen between baseline BNP and subsequent change in BNP other than higher BNP at baseline having a much higher variability in change in BNP. Baseline BNP was strongly predictive of outcome. It might be expected that a large increase in BNP over time would predict poorer prognosis, with the converse true for falling BNP. This proved not to be the case as change in BNP failed to add any further prognostic information. Similar findings have been reported elsewhere (238,239); it appears that a single determination of natriuretic peptide levels at any time point provides higher prognostic discrimination than change in levels, and the findings here would support that.

Thus, baseline BNP and change in eGFR proved to be strong independent predictors of adverse outcome. Combining these two variables did appear to add further prognostic discrimination. Dividing the cohort based on median BNP and further dividing based on change in eGFR provided an incremental increase in adverse outcome, as demonstrated in figure 3.15. Assessing those with BNP below the median, table 3.12 illustrates that a larger fall in eGFR carried an adjusted increased risk of 65% and 53% respectively for all cause mortality and cardiovascular mortality. Looking at those with BNP above the median, we can see that larger fall in eGFR increased the adjusted HR from 1.82 to 2.25 for all cause mortality, and from 2.35 to 2.58 for cardiovascular death. Results from this study indicate that a one off BNP level helps predict prognosis after MI, but that monitoring renal function over time may be a better method of assessing progress.

3.4.1 Limitations

All of the limitations discussed in section 2.4.1 would apply equally to this study. Selection bias caused by loss of patients to follow up and to death between the screening visits is another possible limitation and has been discussed above

3.4.2 Conclusion

Compared to other studies, renal function was relatively stable over time in this post MI cohort. The rate of decline was slightly higher than that reported in the general population but not as high as in the immediate post infarct period. Only very few patients fulfilled the criteria for WRF. The steady nature of renal function is likely to reflect two factors; firstly that this cohort represents a relatively well group of post MI survivors with relatively low overall cardiovascular risk and secondly, that this group of patients were in a clinically stable condition with low levels of physiological and pharmacological stress.

Only baseline renal function predicted subsequent change in renal function but this is probably as a result of regression to the mean; hypertension, DM and LVSD did not predict declining renal function. Chronic change in renal function proved to be predictive of outcome, with larger falls in eGFR (or rise in creatinine) being independently predictive of all cause mortality, and particularly cardiovascular death.

Elevated BNP predicted larger subsequent decline in eGFR. Change in BNP levels did not add further prognostic information over a single determination of levels. A combination of baseline BNP and subsequent change in eGFR provided a stepwise prognostic model.

CHAPTER 4

GP-HEART FAILURE COHORT

4.1 Introduction

Renal disease is very common in HF, with approximately one third to one half of individuals having stage 3 CKD or worse (46-48,89,90). This can be explained by the generally older age group that HF cohorts represent, and also due to adverse activation of the RAAS which is almost pathognomonic of HF. In addition, HF cohorts will have a high prevalence of DM and hypertension, both of which are the leading causes of kidney disease world wide.

As in the rest of the Western world, HF exerts considerable financial and human cost in Scotland. It is estimated that almost 90,000 people in Scotland are living with HF; this number is likely to rise in the next one to two decades as the population increases and ages (8,240), and treatments for MI and HF improve. Prognosis in HF is very poor despite recent improvements in therapies and this prognosis is even worse if there is co-existent CKD; having an eGFR <60ml/min/1.73m^2 carries an adjusted risk of death of about 1.5 (46,85,90). By the time an individual is admitted to hospital with HF, they are more often than not towards the latter end of the disease process. As such, early diagnosis and initiation of HF treatments in the community could have significant benefits. The HF-GP study from the CRI project in Glasgow was concerned with identifying patients in the community with possible HF; close examination of these individuals could help in developing strategies aimed at early out-patient diagnosis of HF. Analysis of this cohort has generated two publications, one which concluded that HF drug trial cohorts are not fully representative of the HF population; the other paper designed a risk score for HF diagnosis utilising BNP (232,233).

Renal function has never been assessed in this cohort. This chapter is concerned with examining the prevalence of renal disease in this Glasgow cohort and assessing its influence

on outcome. The interaction between renal function and BNP will also be addressed as will the ability of renal function to identify HF or LVSD in the community.

4.2 Methods

4.2.1 Patient identification

As detailed elsewhere (232), in 1995, a HF nurse screened 15 randomly selected general practices (GP) in North Glasgow to identify all patients taking ACE-inhibitor, digoxin, or loop diuretic agents. GP case notes were subsequently reviewed to look for more information about clinical and objective signs of HF. The GP was consulted before the patient could be considered eligible for a cardiac examination in a hospital-based clinic.

1194 subjects were identified. After consultation with the general practitioners 235 subjects were excluded from further investigation because they were dead (n = 25), too frail, hospitalized, or residing in a nursing home (n = 173), had moved away from Glasgow (n = 12) or had attended another screening study (n = 25). The first 500 subjects of the remaining 959 eligible subjects who accepted the invitation to attend for the screening visit constituted the study population.

4.2.2 Screening visit

Questionnaire

A self-reported questionnaire was obtained for all subjects giving details of physician diagnosed angina, myocardial infarction, diabetes, stroke, drug therapy, and answers to the Medical Research Council (MRC) Breathlessness questions(234).

Blood pressure

Blood pressure was taken as a mean of two readings, measured with the participant seated (after 5 min rest), on the right arm, with a random zero sphygmomanometer. Serum cholesterol was recorded as the average of two measurements.

Echocardiography

Standard two-dimensional echocardiography (Acuson 128) was carried out with the participant reclining at 40°, in the left lateral position. Images were stored on videotape and analysed on-line. The left-ventricular ejection fraction was calculated by the biplane disc summation method (Simpson's rule) (235). Each ejection fraction is a mean of three cardiac cycles. Echocardiograms were deemed of acceptable quality if 80% or more of the endocardium was visible.

Blood sampling

Blood samples were taken from the antecubital fossa. Analysis for blood glucose was performed. BNP levels were analysed using the Shionogi assay (Shionoria, Japan).

Serum samples were frozen at time of screening. They were subsequently thawed in October 2006 and immediately analysed for creatinine concentration on an Abbott c8000 analyser using a reaction rate Jaffe method (Abbott Diagnostics, US). Serum creatinine levels have been shown to remain stable when samples are stored at very low temperatures for many years (245). Estimated glomerular filtration rate (eGFR) was then calculated for each individual using the Modified Diet in Renal Disease formula [186 x [SerumCreatinine (μmol/L) x $0.0113]^{-1.154}$ x Age $(years)^{-0.203}$ (x 0.742 if female)].

Electrocardiography

The standard 12-lead electrocardiograms (ECGs) were coded independently for atrial fibrillation or sinus rhythm.

4.2.3 Definitions

Hypertension was defined as; a history of high blood pressure; a measured blood pressure of more than 160mmHG systolic, more than 95mmHG diastolic, or both; current treatment with anti-hypertensives or; a combination of these factors.

Diabetes mellitus was defined as: a history of diabetes; current treatment with oral hypoglycaemic agents and/or insulin; a blood glucose level greater than 11.0 mg/dL or; a combination of these factors.

Ischaemic heart disease was defined as the presence of angina or previous MI.

Left ventricular systolic dys function was defined as LVEF of less than 35%.

Renal impairment was defined using both eGFR and serum creatinine. With eGFR, current guidelines regarding CKD classification were used(24); For CKD stage 1 and 2, guidelines indicate that there must be evidence of kidney damage in the form of proteinuria or haematuria; urinalysis was not available to us and thus we classified patients as CKD stage 1 or 2 based solely on their calculated eGFR. Renal impairment using serum creatinine was divided based on published cut-offs (88,241) for mild (88.4 to 132.6μmol/l) moderate (132.6 to 176.8μmol/l) and severe (>176.8μmol/l)

Criteria of HF

Hospital diagnosed HF (HF-Hosp) was based on explicit information from an outpatient visit or a hospital admission where the patient had been given the diagnosis of HF, an equivalent diagnostic term, or if objective tests had shown significant and symptomatic LV systolic dysfunction, valvulopathy or cardiomyopathy.

GP diagnosed HF (HF-GP) was diagnosed in the case of a history of breathlessness, swollen ankles, fluid retention, or an abnormal chest X-ray in a patient in combination with a current prescription of a loop diuretic. An abnormal chest X-ray was a cardiothoracic ratio (CTR) > 50%, enlarged left ventricle, pleural effusion, upper lobe venous diversion, or interstitial or alveolar oedema.

HF patients were a combination of HF-GP and HF-Hosp patients.

Non-HF patients were defined as the remaining subjects who received HF therapy but did not meet the criteria for Hospital-HF or HF-GP.

4.2.4 Deaths

The date and cause of death was identified by flagging each patient's record with the Registrar General for Scotland on December 31, 2000. From the information on death certificates, two experienced cardiologists (Professor Henry Dargie, Dr Theresa McDonagh) coded the deaths as cardiovascular, cancer, respiratory or other. The cardiovascular deaths were further sub classified as being due to MI, HF, cerebrovascular disease or other. Where

information on death certificates was missing or incomplete, the death was labelled as "uncoded".

4.2.5 Statistical analysis

The majority of continuous values were normally distributed and means were compared using an unpaired t-test or ANOVA as appropriate. The exceptions were serum creatinine, NT-ANP and BNP levels, which were compared between groups using a Mann-Whitney test or logarithmically transformed as necessary. Categorical variables were compared using χ^2 test. Correlation between continuous variables was assessed using Pearson's technique. ROC analysis was used to assess the ability of natriuretic peptides and creatinine to identify LVSD within the cohort, and the ability of serum creatinine to correctly identify individuals with stage 3 CKD or worse.

Kaplan-Meyer analysis was used to compare survival and cardiovascular deaths between groups, with subsequent log-rank testing. Survival between groups was then assessed using Cox regression, and hazard ratios (HR) were calculated. Univariate analysis was performed initially, followed by multivariate analysis; variables that were significantly associated with mortality from the univariate analyses ($p < 0.10$) were included in multivariate models. The specific variables included in the multivariate analysis for all cause mortality were age, gender, previous MI, AF, hypertension, DM, COPD, HF, ACE-inhibitor therapy, loop diuretic therapy, aspirin therapy and digoxin therapy. The same variables were used in the multivariate model for cardiovascular death, with the exception of DM, ACE-inhibitor therapy and aspirin therapy. These models were used for subsequent analysis of BNP and renal function.

All analysis was performed using SPSS or Minitab. A p value of less than 0.05 was considered statistically significant.

4.3 Results

4.3.1 Baseline characteristics

Five hundred individuals were selected to undergo screening. Their baseline characteristics are detailed in Table 4.1.

	Baseline characteristics
n	500
Age (years)	68.5 ± 11.6
Age range (years)	31.6 – 91.2
Male (%)	33.8
Height (cm)	160.2 ± 9.4
Weight (kg)	71.5 ± 16.0
BMI (kg/m²)	27.8 ± 5.5
Obese (%)	30.8
Systolic BP (mmHG)	147.3 ± 26.2
Diastolic BP (mmHG)	79.2 ± 14.6
Myocardial infarction (%)	28.5
Angina (%)	33.7
Atrial Fibrillation (%)	15.8
NYHA (%)	
I	46.7
II	7.5
III	13.1
IV	32.7
LVEF (%)	48.4 ± 11.3
LVSD (%)	12.6
Hypertension (%)	56.7
Diabetes Mellitus (%)	11.0
Asthma (%)	12.0
Arthritis (%)	49.9
COPD (%)	38.9
Medications (%)	
Loop diuretic	58.2
Any diuretic	75.3
ACE-Inhibitor	36.0
Beta blocker	16.1
Digoxin	19.5
Spironolactone	2.2
Aspirin	35.1
NSAID	14.7
BNP (pg/ml)	42.0 (84.8)
NT-ANP (pg/ml)	4.9 (6.4)

Table 4.1: Baseline characteristics of GP-Heart failure cohort

This was an elderly cohort, with a mean age of 68.5 ± 11.6 years; almost two thirds were female. There was no difference between the sexes in mean age (male 67.9 ± 10.6 v female

68.5 ± 12.0 years, p =0.57). Not unexpectedly, there was a considerable history of established cardiovascular disease, with over one quarter having a history of previous MI and one third reporting angina. 15.8% of the cohort had AF and 12.6% of those who underwent echocardiography had an ejection fraction of less than 35%.

The majority of the cohort (53.3%) had some degree of exertional breathlessness with 32.7% having breathlessness at rest or on minimal exertion (NYHA IV). There were considerable levels of co-morbidity with high rates of obesity, hypertension, COPD and arthritis.

Of the study cohort, one hundred and ninety nine (39.8%) were fulfilled the criteria of heart failure (HF), leaving three hundred and one (60.2%) individuals who did not have heart failure (non-HF). One hundred and two of those with HF fulfilled the criteria of hospital diagnosed HF (HF-Hosp) and ninety-seven had GP diagnosed HF (HF-GP). The baseline characteristics as a function of HF classification is shown in Table 4.2.

The non-HF patients were much younger than those with HF, although the gender mix did not differ. Non-HF patients had much lower levels or cardiovascular disease such as previous MI, angina or AF but had a significantly higher rate of hypertension, as well as a higher mean systolic and diastolic blood pressure. There was no significant difference between the non-HF and HF patients in beta blocker and ACE-inhibitor use although the non-HF patients were much less likely to be taking diuretics, digoxin or aspirin. Non-HF patients had a more favourable NYHA distribution.

	Non-HF	Heart Failure HF-Hosp	HF-GP	p value Non v HF	p value Hosp v GP HF
n	301	102	97		
Age (years)	66.4 ± 12.2	73.1 ± 9.1	70.1 ± 10.0	< 0.001	0.028
Male (%)	34.2	45.1	20.6	0.807	< 0.001
BMI (kg/m²)	27.8 ± 5.5	26.9 ± 5.2	28.6 ± 5.7	0.860	0.025
Obese (%)	33.2	21.5	32.9	0.149	0.07
Systolic BP (mmHG)	150.7 ± 25.9	139.9 ± 25.6	144.3 ± 26.1	< 0.001	0.23
Diastolic BP (mmHG)	81.6 ± 13.6	74.4 ± 16.5	77.3 ± 14.2	< 0.001	0.017
MI (%)	19.9	49.5	33.0	<0.001	0.022
Angina (%)	22.9	51.5	48.5	<0.001	0.72
AF (%)	11.6	21.6	22.7	0.002	0.85
NYHA (%)					
I	57.1	23	37	< 0.001	0.06
II	7.0	6	9		
III	7.4	25	15		
IV	26.9	45	36		
Hypertension (%)	63.8	42.6	49.5	< 0.001	0.30
Diabetes Mellitus (%)	9.6	15.9	10.3	0.23	0.26
Asthma (%)	12.3	11.9	11.3	0.80	0.93
Arthritis (%)	48.2	48.5	56.7	0.37	0.22
COPD (%)	34.0	48.4	44.6	0.016	0.79
Medications (%)					
Loop diuretic	35.5	85.2	100	<0.001	<0.001
Any diuretic	57.5	97.3	100	<0.001	0.004
ACE-Inhibitor	37.2	50.5	16.5	0.42	<0.001
Beta blocker	20.6	6.9	17.7	0.12	0.013
Digoxin	13.0	39.6	18.6	<0.001	0.001
Spironolactone	2.3	3.0	1.0	0.82	0.33
Aspirin	27.8	51.5	40.2	<0.001	0.12
NSAID	15.1	8.9	19.6	0.94	0.029

Table 4.2 Baseline characteristics of GP-Heart Failure cohort as a function of HF status.

In the patients with HF, there were a number of differences between the HF-Hosp and HF-GP groups. The HF-Hosp patients were older, leaner and had a higher proportion of males. They had a much higher rate of previous MI than the HF-GP patients although rates of angina and AF did not differ. There was a trend towards more severe NYHA status in the HF-Hosp group.

Diuretic use was actually higher in the HF-GP patients although the vast majority of patients in either cohort were taking an oral diuretic. The HF-Hosp patients were three times more likely to be taking an ACE-inhibitor and twice as likely to be taking digoxin but less than half

as likely to be taking a beta-blocker. NSAID use was higher in the HF-GP group, although the rate of arthritis was not.

4.3.2 Echocardiography

ECHO results were not available for all patients; only three hundred and fifty had ejection fractions calculated using Simpson's technique and not all of these individuals has LV or LA dimensions recorded. As shown in Table 4.3, the overall rate of LVSD was 12.6% with a slightly higher proportion demonstrating LV dilatation. Over one quarter of the cohort had LV hypertrophy. Over half of the patient's demonstrated LA dilatation and one in seven had evidence of valvular disease.

	All	Non-HF	HF-Hosp	HF-GP
n	500	301	102	97
n with Simpsons	350	210	73	67
LVEF (%)	48.7 ± 11.3	50.8 ± 9.8	40.5 ± 12.6	49.7 ± 9.9
LVSD (%)	12.6	6.2	32.9	10.7
LV systolic function* (%)				
Normal	31.4	35.7	15.1	35.8
Mild	34.0	39.5	17.8	34.3
Moderate	22.0	18.6	34.2	19.4
Severe	12.6	6.2	32.9	10.4
n with LV dimensions	230	135	52	43
LVEDD (cm)	4.9 ± 0.7	4.8 ± 0.6	5.3 ± 0.9	4.8 ± 0.6
Dilated LV (%)	16.5	10.4	32.7	16.3
LV hypertrophy (%)	28.3	20.0	48.1	30.2
n with LA dimensions	340	203	66	71
Dilated LA (%)	55.0	48.3	69.7	60.6
Valve disease	14.3	9.0	23.3	20.9
Prosthetic valve	6.9	4.3	9.6	11.9

Table 4.3: Baseline ECHO findings of cohort as a whole, and as a function of HF classification. (*LV function as per BSE classification)

As shown in Table 4.3, the non-HF patients had the most favourable ECHO findings with low rates of LVSD, LV hypertrophy and valvular disease. HF-GP patients had a comparable mean LVEF to the non-HF patients although almost twice the rate of LVSD. The HF-Hosp patients had the most severe disease as demonstrated by ECHO; mean LVEF was approximately ten

points lower than both the non-HF and HF-GP patients, with one third of HF-Hosp patients having LVSD. HF-Hosp patients also had higher rates of LV dilatation and hypertrophy. HF-GP and HF-Hosp patients had very similar levels of LA dilatation and valvular disease.

In the cohort as a whole, males had significantly lower LVEF than females (44.2 ± 11.5 v 50.7 ± 10.4 %, p< 0.001). LVEF was significantly lower in patients with previous MI (41.0 ± 11.5 v 51.7 ± 9.4%, p < 0.001) and in those with angina (44.6 ± 11.6 v 50.3 ± 10.6%, p < 0.001). Diabetics had a lower LVEF than non-diabetics (44.9 ± 11.0 v 48.9 ± 11.2%, p = 0.049) although those with hypertension (47.8 ± 11.9 v 49.1 ± 10.6%, p = 0.29) and AF (48.5 ± 11.3 v 47.9 ± 10.8%, p = 0.73) had similar LV function to normotensives and those in sinus rhythm respectively.

Forty four patients had a LVEF less than 35%, i.e. LVSD; these patients were twice as likely to be male (61.6 v 31.0%, p < 0.001). Age did not differ between those with LVSD and those without (70.6 ± 9.8 v 67.6 ± 12.2 years, p = 0.15), nor did BMI (27.1 ± 5.3 v 27.3 ± 4.8 kg/m^2, p = 0.83). Patients with LVSD had a significantly higher proportion taking ACE-inhibitors (60.5 v 36%, p = 0.002) and loop diuretics (74.4 v 55.7%, p = 0.02) compared to the rest of the group and there was a trend toward higher use of digoxin (25.6 v 15.1%, p =0.08); however, beta blocker use was much lower in those with LVSD, but this was not statistically significant (7.7 v 17.0%, p = 0.08).

4.3.3 Natriuretic peptides

Four hundred and fifty nine patients had results available for natriuretic peptides, namely NT-ANP and BNP. These were both non-normally distributed, as shown in Figure 4.1. Median

(IQ range) BNP and NT-ANP levels for the cohort were 42.0 (84.8) pg/ml and 4.9 (6.4) pg/ml respectively. LogBNP and logANP correlated strongly ($r = 0.709$, $p < 0.001$)

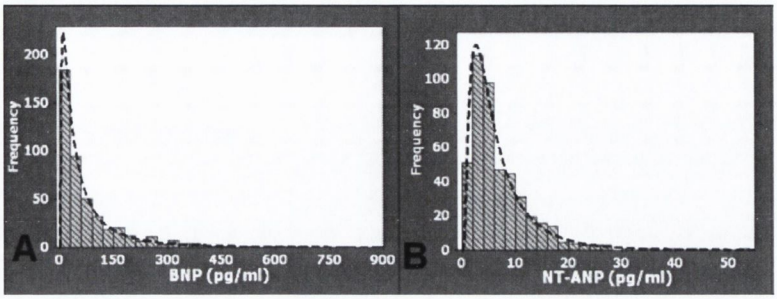

Figure 4.1: Histograms of natriuretic peptide distribution in cohort (A) BNP (B) NT-ANP

Higher natriuretic peptide concentrations were seen with older age, as shown in figure 4.2; age correlated positively with both logNT-ANP ($r = 0.474$, $p < 0.001$) and with logBNP ($r = 0.456$, $p < 0.001$). There was no significant difference between males and females in median (IQR) levels of either BNP (48.5 (99.1) v 39.2 (77.4) pg/ml, $p = 0.12$) or NT-ANP (5.3 (6.1) v 4.9 (6.8) pg/ml, $p = 0.14$).

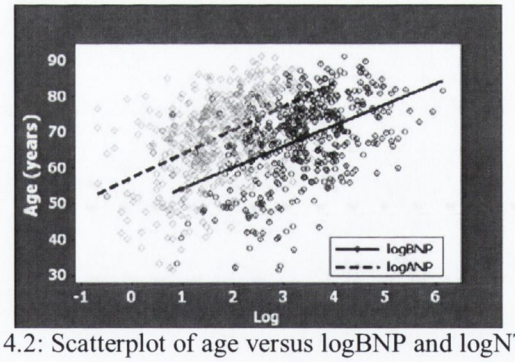

Figure 4.2: Scatterplot of age versus logBNP and logNT-ANP

Patients with established cardiovascular disease had much higher levels of natriuretic peptides. Those with previous MI had significantly higher Median (IQR) levels of NT-ANP (6.5 (7.3) v 4.5 (5.8) pg/ml, $p < 0.001$) and BNP (69.4 (96.2 v 33.0 (67.6) pg/ml, $p < 0.001$), compared to those without MI; a similar difference was seen between those with angina and those without in both NT-ANP (7.0 (7.0) v 4.4 (5.4) pg/ml, $p < 0.001$) and BNP (59.0 (102.4)

v 32.6 (70.6) pg/ml, $p < 0.001$). A marked difference in natriuretic peptides levels was also demonstrated between those in AF and those in sinus rhythm, with AF patients having twice the median (IQR) levels of NT-ANP (9.7 (8.9) v 4.5 (5.4) pg/ml, $p < 0.001$) and almost four times as much BNP (127.0(133.4) v 33.3 (63.0) pg/ml, $p < 0.001$).

Hypertensive patients had lower levels of both NT-ANP (4.4 (5.8) v 6.5 (6.0) pg/ml, $p = 0.004$) and BNP (33.3 (80.4) v 52.5 (87.6), $p = 0.005$), compared to normotensives whilst there was no difference between diabetic and non-diabetic patients in either BNP ($p = 0.43$) or NT-ANP ($p = 0.37$).

There was a significant association between LV systolic function and the natriuretic peptides. LVEF correlated weakly, but significantly, with both logBNP ($r = -0.281$, $p < 0.001$) and logNT-ANP ($r = -0.239$, $p < 0.001$). Median (IQ range) BNP concentration (147.0 (229.1) v 37.9 (60.6) pg/ml, $p<0.001$) and NT-ANP concentration (10.2 (10.8) v 4.8 (5.6) pg/ml, $p < 0.001$) were much higher in those with LVSD compared to those without (see figure 4.3).

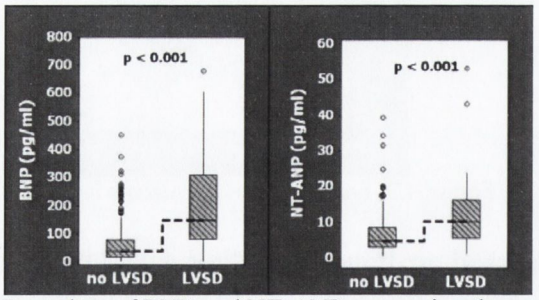

Figure 4.3: Box-plots of BNP and NT-ANP comparing those with LVSD with those without LVSD

Patients with HF had substantially elevated levels of natriuretic peptides, compared to non-HF patients. BNP levels were twice as high in HF patients (64.8 (114.9) v 32.3 (61.8) pg/ml, $p < 0.001$) and NT-ANP levels were fifty percent higher (6.6 (7.0) v 4.3 (5.8) pg/ml, $p <$

0.001). Within the HF group, HF-Hosp patients had higher levels of BNP compared to HF-GP patients (77.8 (126.6) v 45.4 (99.2) pg/ml, p =0.004); NT-ANP levels were also higher but not significantly so (7.5 (7.3) v 5.6 (7.3) pg/ml, p = 0.11). NYHA classification did not appear to have a significant association with natriuretic peptide levels. In the cohort as a whole, there was a trend toward a higher BNP in NHYA IV compared to NYHA I (see figure 4.4). Looking specifically at those with HF, no such trend was seen, with median BNP being very similar regardless of NYHA class.

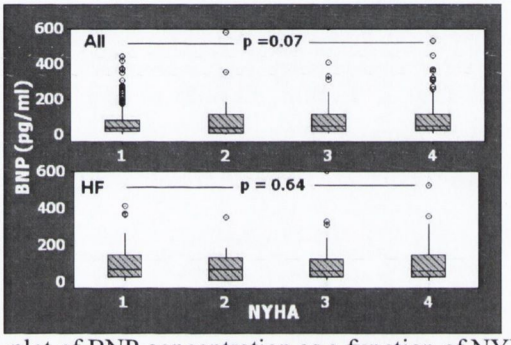

Figure 4.4: Box-plot of BNP concentration as a function of NYHA class in the entire cohort (top) and in those with HF (bottom)

4.3.4 Renal function

4.3.4.1 eGFR

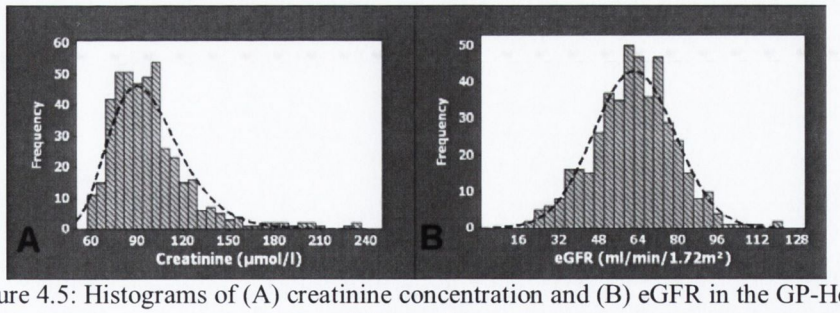

Figure 4.5: Histograms of (A) creatinine concentration and (B) eGFR in the GP-Heart failure cohort

Mean calculated eGFR for the cohort was 62.2 ± 16.4 ml/min/1.73m² and ranged from 121.2 to 18.9 ml/min/1.73m², as demonstrated in figure 4.5B. Almost half of the cohort (43.6%) had an eGFR <60 ml/min/1.73m²; the distribution of CKD stages 1-4 is shown in figure 4.6.

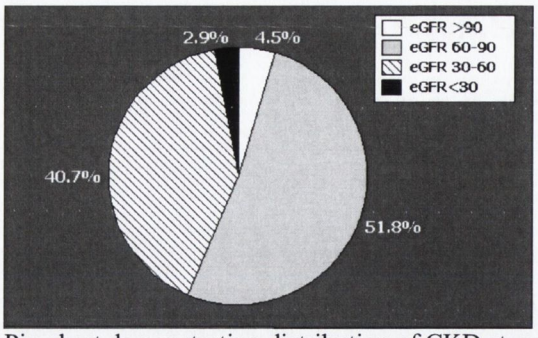

Figure 4.6: Pie-chart demonstrating distribution of CKD stages in cohort

A definite pattern was seen between increasing age and lower eGFR; age correlated negatively with eGFR ($r = -0.40$, $p < 0.001$, see figure 4.7). Women had a significantly lower mean eGFR than men (59.7 ± 15.7 v 67.0 ± 16.5 ml/min/1.73m^2, $p < 0.001$); indeed, almost half of the women in the cohort (49.6%) has CKD stage 3 or worse, compared to 32.2% of men.

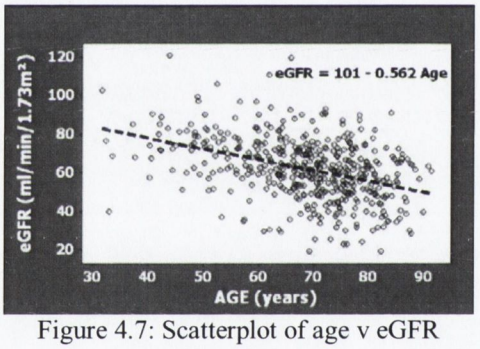

Figure 4.7: Scatterplot of age v eGFR

Those patients in the cohort with established cardiovascular disease had evidence of poorer renal function. Although eGFR did not correlate with LVEF ($r = 0.045$, $p = 0.43$), there was a trend toward those with LVSD having significantly lower mean eGFR (57.7 ± 15.3 v 62.6 ± 16.5 ml/min/1.73m^2, $p = 0.07$). Patients with previous myocardial infarction had a lower eGFR than those without (59.8 ± 16.1 v 63.2 ± 16.3 ml/min/1.73m^2, $p = 0.047$), as did patients reporting angina, compared to those without (59.5 ± 15.1 v 63.6 ± 16.7 ml/min/1.73m^2, $p = 0.01$). Similarly, patients in AF had poorer renal function than those in sinus rhythm (58.7 ± 12.5 v 62.8 ± 16.9 ml/min/1.73m^2, $p = 0.02$). Renal function did not

differ significantly between hypertensive and normotensive patients (mean eGFR 62.9 ± 17.3 v 61.5 ± 14.8 ml/min/1.73m² respectively, p = 0.38), nor did diabetics and non-diabetics have significantly different mean eGFRs (60.5 ± 17.7 v 62.5 ± 16.1 ml/min/1.73m² respectively, p = 0.46).

As shown in table 4.4, diuretic use was associated with lower eGFR, as was aspirin. NSAID and beta blocker use had no association with renal function although ACE-inhibitor use was actually associated with better renal function.

	On medication	Not on medication	p value
ACE-I	65.1 ± 17.3	60.5 ± 15.4	0.007
Beta blocker	59.6 ± 15.7	62.8 ± 16.4	0.13
Loop diuretic	58.3 ± 15.2	67.4 ± 16.2	< 0.001
Any diuretic	59.4 ± 15.3	68.4 ± 16.5	< 0.001
Digoxin	59.3 ± 14.8	62.8 ± 16.5	0.06
Spironolactone	57.8 ± 23.6	62.3 ± 16.1	0.61
Aspirin	60.1 ± 16.7	63.3 ± 15.9	0.047
NSAID	60.3 ± 15.3	62.5 ± 16.4	0.29

Table 4.4: Mean eGFR 9ml/min/1.73m²) per prescribed medication in GP Heart Failure cohort.

The baseline characteristics of the cohort as a function of their CKD status is highlighted in table 4.5. Increasing age and higher proportion of females was seen with increasing CKD stage. There was a trend toward increased levels of MI, angina, AF and poor LV function as renal function deteriorated. COPD was significantly more prevalent in CKD stages 3 and 4. Higher CKD stage was also associated with increased use of diuretics, although ACE-inhibitors were more commonly prescribed in patients with CKD stage 1 and 2.

	eGFR >90	eGFR 60 - 90	CKD stage 3	CKD stage 4	p value
n	20	229	180	13	
Age (years)	59.3 ± 12.8	65.6 ± 12.0	72.0 ± 9.6	75.4 ± 8.1	< 0.001
Male (%)	60.0	39.7	25.6	23.1	< 0.001
BMI (kg/m²)	28.1 ± 7.2	28.2 ± 5.6	27.4 ± 5.1	28.3 ± 4.5	0.53
Obese (%)	25.0	36.2	25.6	38.5	0.11
Systolic BP (mmHG)	149.5 ± 20.2	148.1 ± 27.3	146.0 ± 27.0	148.0 ± 24.0	0.85
Diastolic BP (mmHG)	85.9 ± 11.2	82.0 ± 14.0	75.4 ± 14.3	79.2 ± 16.6	< 0.001
MI (%)	20.0	24.5	33.9	38.5	0.11
Angina (%)	15.0	29.7	38.9	38.5	0.06
AF (%)	0.0	14.8	17.8	0.0	0.07
LVEF (%)	51.9 ± 6.9	48.5 ± 11.2	49.3 ± 11.1	40.9 ± 12.5	0.10
LVSD (%)	0.0	8.3	8.9	23.1	0.11
Hypertension (%)	75.0	55.0	56.1	61.5	0.32
DM (%)	20.0	9.6	11.1	23.1	0.22
Asthma (%)	10.0	11.8	13.9	7.7	0.87
Arthritis (%)	40.0	44.5	58.3	46.2	0.04
COPD (%)	35.0	29.7	40.6	61.5	0.009
Medications (%)					
Loop diuretic	20.0	49.8	68.3	76.9	< 0.001
Any diuretic	35.0	62.4	78.3	84.6	< 0.001
ACE-Inhibitor	65.0	38.0	30.6	30.8	0.01
Beta blocker	15.0	13.1	20.0	7.7	0.24
Digoxin	5.0	17.9	20.6	15.4	0.43
Spironolactone	0.0	1.7	1.7	7.7	ns
Aspirin	35.0	30.1	41.1	30.8	0.16
NSAID	5.0	15.3	16.7	7.7	0.54

Table 4.5: baseline characteristics of GP Heart Failure cohort as a function of baseline CKD status.

4.3.4.2 Creatinine

Creatinine levels were available for four hundred and forty two patients; median creatinine concentration was 93.0 μmol/l and ranged from 58.3 to 235.0 μmol/l. The non-normal distribution of creatinine concentration is shown in figure 4.5A. 40.4% of the cohort had normal renal function based on their creatinine level (<88.4μmol/l) whilst 50.9% had mild renal impairment (88.4 – 132.6μmol/l). Only 5.7% had moderate renal impairment (132.6 – 176.8μmol/l) and 2.9% had severe impairment (>176.8μmol/l).

Thus the cohort as a whole had relatively poor renal function, perhaps not fully reflected by creatinine levels. Indeed, taking an eGFR <60 ml/min/1.73m² as the gold standard test of

renal impairment, figure 4.8 demonstrates how accurately creatinine concentration by itself identifies individuals with significant renal impairment.

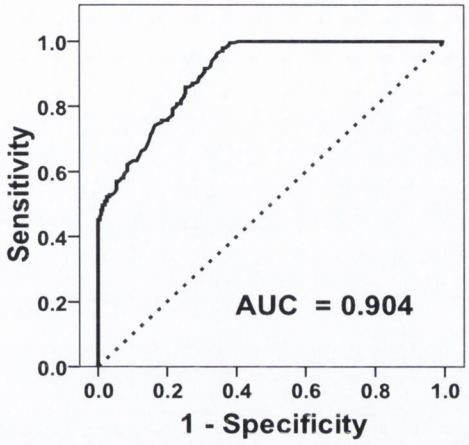

Figure 4.8: ROC curve assessing ability of serum creatinine level to identify patients with renal impairment (defined as eGFR < 60ml/min/1.73m²)

Using the cut-offs for mild, moderate and severe renal impairment based on serum creatinine, 12 individuals with an eGFR of < 60ml/min/1.73m² would have been misclassified as having normal renal function; these individuals were exclusively elderly females (mean age 74.9 years) and represent 6.2 % of all individuals with CKD stage 3 or worse. Conversely, 82 individuals (95% male, mean age 66.2) were classified as having mild renal impairment, even though they had eGFR > 60ml/min/1.73m².

4.3.4.3 Renal function and HF

Non-HF patients had significantly better renal function than patients with HF (mean eGFR 65.4 ± 16.1 v 56.9 ± 15.3 ml/min/1.73m², $p < 0.001$) and had a smaller proportion of patients with stage 3 CKD or worse (35.7 v 56.6%, $p < 0.001$). Within those patients with HF, HF-Hosp patients had a lower eGFR (55.0 ± 16.3 v 58.7 ± 14.2 ml/min/1.73m², $p = 0.12$) than HF-GP patients and a higher proportion of patients with stage 3 CKD or worse (59.7 v 53.4%, $p = 0.41$), but not significantly so.

NYHA class showed no correlation to renal function in the cohort as a whole, or specifically in those with HF. Mean eGFRs for NYHA class I, II, III, IV were 63.0, 60.0, 64.7, 60.4 ml/min/1.73m^2 respectively ($p = 0.25$) for the entire cohort; specifically looking at those with HF, mean eGFRs were 54.9, 55.4, 62.6, 56.2 ml/min/1.73m^2 ($p = 0.21$).

4.3.4.4 Renal function and natriuretic peptides

Renal function had a strong inverse relationship with natriuretic peptide concentrations, as demonstrated in figure 4.9. eGFR correlated negatively with both logNT-ANP ($r = -0.420$. $p < 0.001$) and logBNP ($r = -0.340$, $p < 0.001$).

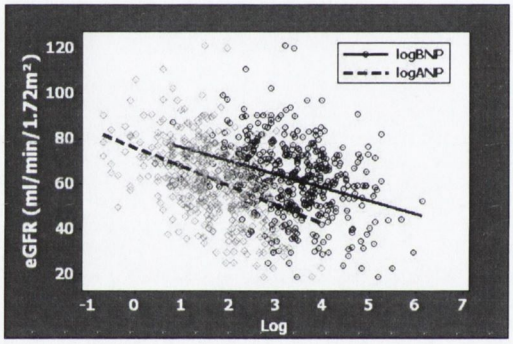

Figure 4.9: Scatterplot of eGFR versus logBNP and logNT-ANP

4.3.5 Renal function to identify HF or LVSD

Using renal function to identify patients in the cohort with either HF or LVSD had mixed results. Both eGFR and creatinine proved to be mediocre tests at identifying HF, with eGFR proving slightly better (see figure 4.10); however, it is worth noting that they compared favorably to both NT-ANP and BNP at identifying HF (see table 4.6).

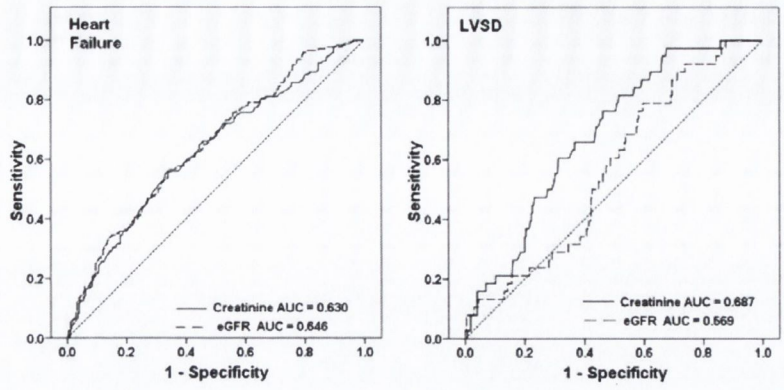

Figure 4.10: ROC curves demonstrating ability of serum creatinine and calculated eGFR to identify Heart Failure (left) and LVSD (right).

eGFR proved poor at identifying LVSD, although creatinine did somewhat better (figure 4.10); natriuretic peptides, and specifically BNP, had a much higher AUC (table 4.6). eGFR and creatinine again compared favorably to natriuretic peptides at identifying the most ill patients in the cohort, i.e. the HF-Hosp patients. However, neither renal function nor natriuretic peptides were good methods of identifying HF-GP patients from the cohort as a whole, or separating HF-GP from non-HF patients.

	eGFR	Creatinine	NT-ANP	BNP
Heart Failure	0.646	0.630	0.640	0.653
LVSD	0.569	0.687	0.718	0.791
HF-Hosp	0.645	0.700	0.650	0.689
HF-GP	0.580	0.504	0.566	0.547
HF-GP*	0.623	0.555	0.605	0.596

Table 4.6: ROC analysis comparing ability of creatinine, eGFR, BNP and NT-ANP to identify subgroups from within the entire cohort. (*distinguishing HF patients from Non-HF and HF-GP patients)

4.3.6 Outcome

Mean follow-up was for 10.8 ± 0.4 years. Between the screening visit in 1995 and the end of 2006, two hundred and twenty four (44.8%) patients had died. As shown in Figure 4.11, the rate of death was linear throughout the follow up period.

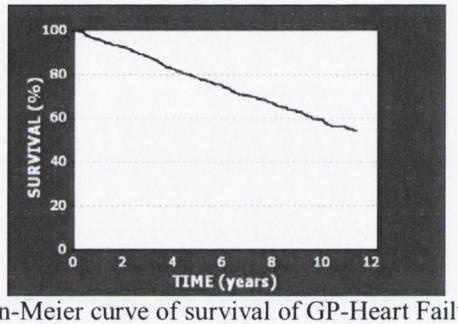

Figure 4.11: Kaplan-Meier curve of survival of GP-Heart Failure cohort through out the 11 year follow up period.

The deaths were coded thus:

- Cardiovascular deaths 128 (57.1% of all deaths)
- Cancer deaths 42 (18.8%)
- Respiratory deaths 25 (11.2%)
- Other 29 (12.9%)

Of the cardiovascular deaths, forty seven (36.7%) were attributed to a MI, thirty-five (27.3%) to HF and twenty six (15.6%) to a cerebrovascular accident. In the deaths due to cancer, twenty one (50%) involved a lung primary, nine (21.4%) originated from the gastrointestinal tract, four (9.5%) were from the urogenital tract, two (4.8%) from breast and the remaining six (14.2%) were from other sources including lymphoma, larynx and unknown.

4.3.6.1 All cause mortality.

Unsurprisingly, increasing age was associated with an increased mortality rate; those younger than 60 years old had a crude mortality of less than 20%, compared to a crude mortality of

almost 70% in those older than 80 years old (see figure 4.12). Although there was no significant age difference between the genders, men had a significantly higher rate of mortality than women (figure 4.12).

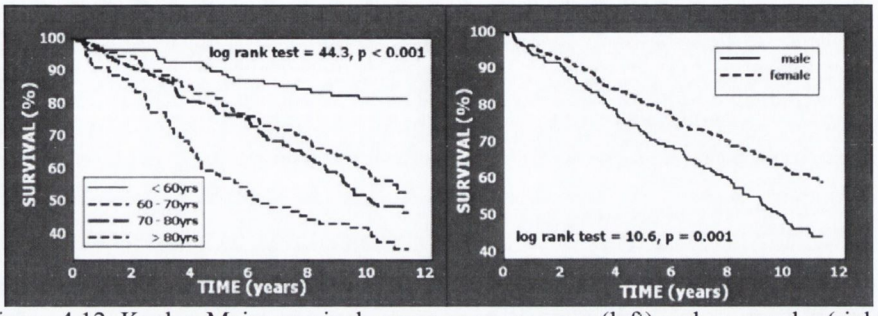

Figure 4.12: Kaplan-Meier survival curves per age group (left) and per gender (right)

Those with established cardiovascular disease also had a poorer long term outcome (figure 4.13). Patients with previous MI had a significantly higher mortality rate than those without MI, although it is interesting that angina appears to have had no influence on outcome. Patients with atrial fibrillation had poorer outcome than those in sinus rhythm.

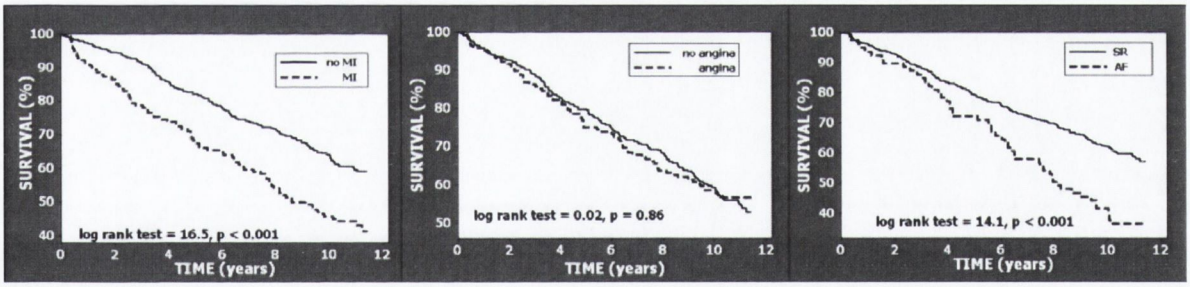

Figure 4.13: Kaplan-Meier survival curves as a function of previous MI (left), reported angina (centre) and atrial fibrillation (right) [SR, sinus rhythm; AF, atrial fibrillation]

Hypertensive patients actually had a better long term outcome than normotensive individuals, although both diabetes mellitus and COPD carried poor prognosis in terms of all cause mortality (figure 4.14).

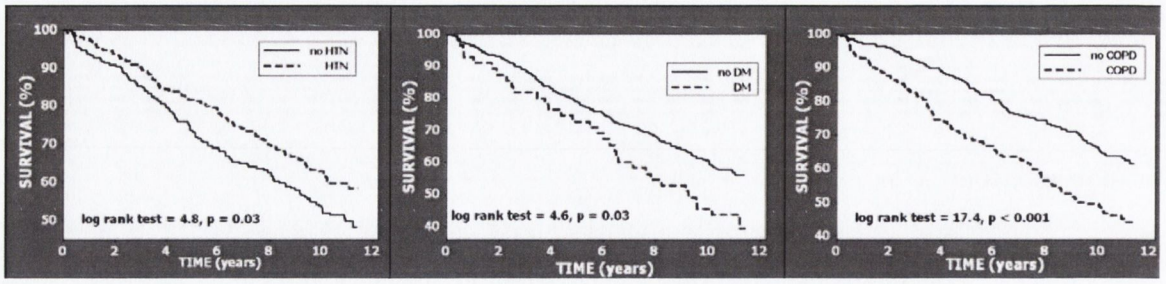

Figure 4.14: Kaplan-Meier survival curves as a function of hypertension (left), diabetes mellitus (centre) and COPD (right).

Medication use at screening reflects co-existent illness: thus individuals taking loop diuretic and digoxin had a poorer long term outcome. Aspirin use was also associated with increased all cause mortality. Beta blockers had no association with long term outcome but ACE-inhibitor use was associated with fewer deaths over the follow up period. NSAID use had no bearing on outcome. Kaplan-Meier curves for survival as a function of baseline medication are shown in figure 4.15.

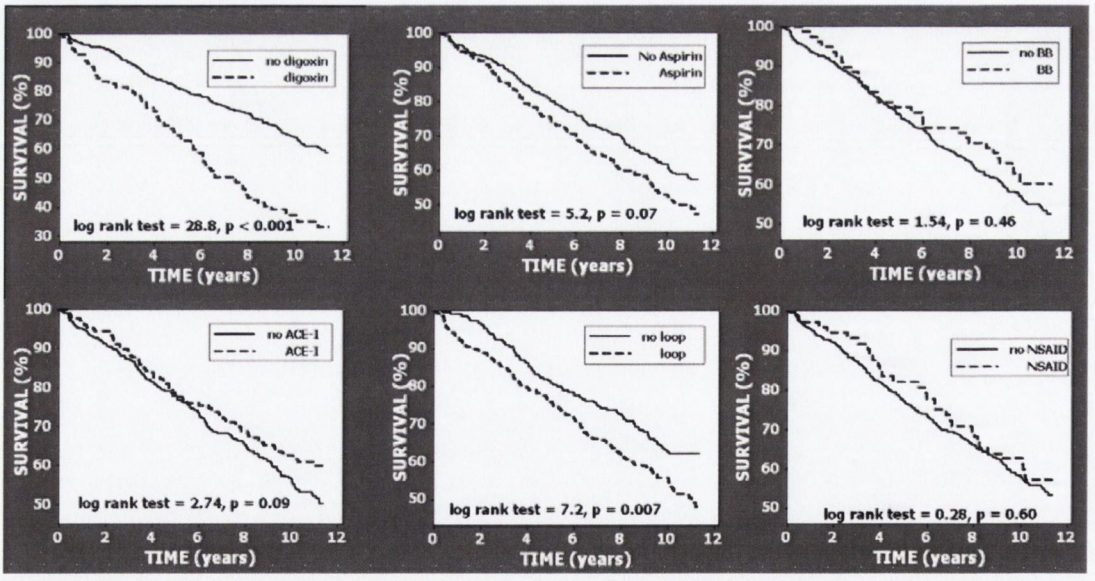

Figure 4.15: Kaplan-Meier survival curves as a function of prescribed medications: digoxin (top left), aspirin (top centre), beta blocker (top right), ACE-inhibitor (bottom left), loop diuretic (bottom centre) and NSAID (bottom right).

4.3.6.2 Cardiovascular death

Cardiovascular outcome followed a similar pattern to all cause mortality. Increasing age and male gender were both associated with increased rates of cardiovascular death (figure 4.16).

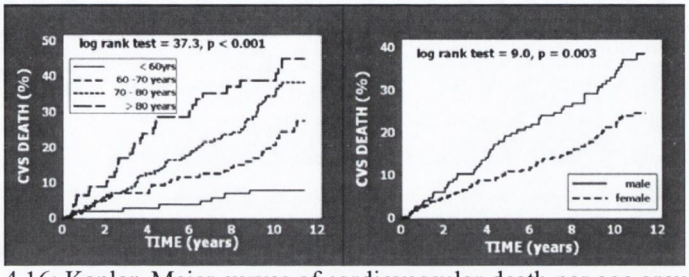

Figure 4.16: Kaplan-Meier curves of cardiovascular death per age group (left) and per gender (right).

Unsurprisingly, both previous MI and AF carried increased risk of cardiovascular death but angina had no significant correlation with long term cardiovascular outcome (figure 4.17).

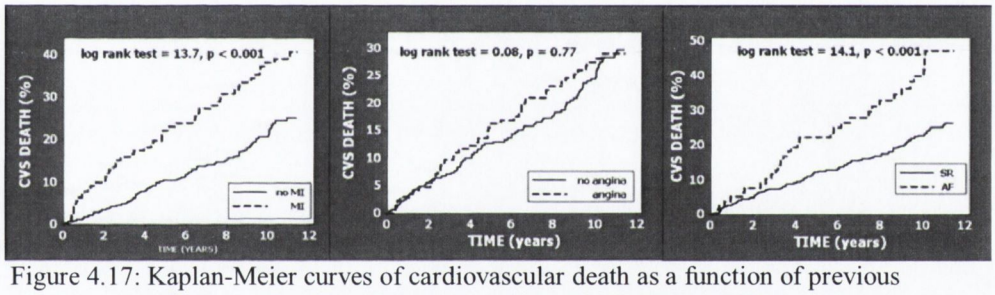

Figure 4.17: Kaplan-Meier curves of cardiovascular death as a function of previous MI (left), reported angina (centre) and atrial fibrillation (right)

Hypertension was actually associated with a reduced risk of cardiovascular death (figure 4.18) but COPD, as with all cause mortality, carried a poor prognosis with regard to cardiovascular death. The rate of cardiovascular death in diabetics was higher than in non-diabetics bit not significantly so (figure 4.18).

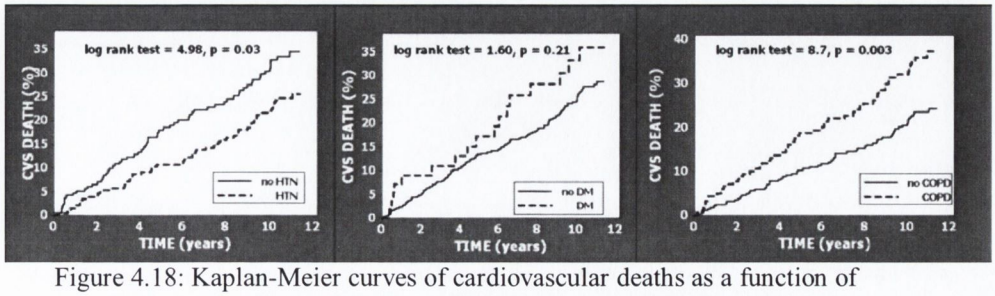

Figure 4.18: Kaplan-Meier curves of cardiovascular deaths as a function of hypertension (left), diabetes mellitus (centre) and COPD (right).

As with all cause mortality, both loop diuretics and digoxin were associated with increased rates of cardiovascular death. Aspirin use had a higher rate of cardiovascular death but not significantly so, and beta-blockers had no correlation with outcome. There were (non-statistically) fewer cardiovascular deaths with ACE-inhibitor use. NSAID use had a very low rate of cardiovascular death in the first six to eight years of follow up, but this increased after this time resulting in an overall neutral correlation with long term cardiovascular outcome. Kaplan-Meier curves for cardiovascular death as a function of baseline medication are shown in figure 4.19.

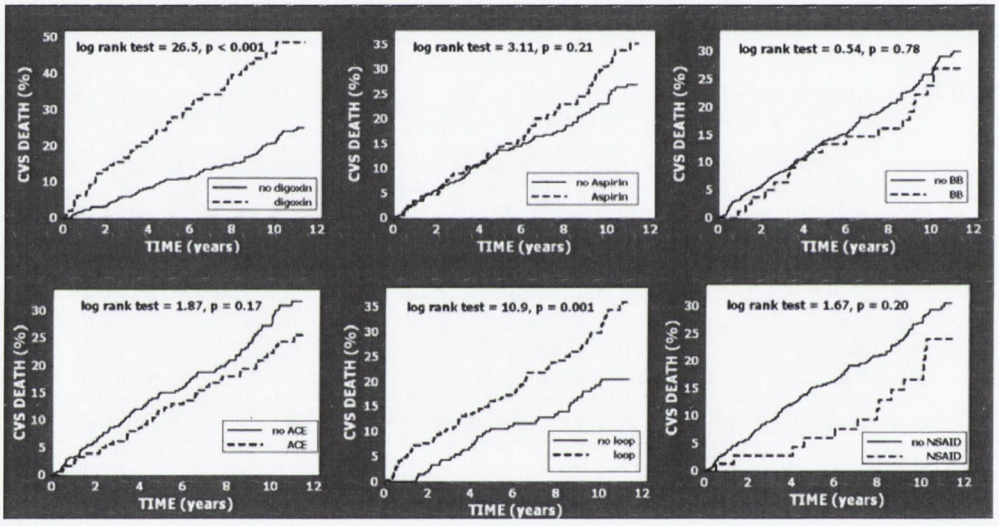

Figure 4.19: Kaplan-Meier curve of cardiovascular deaths as a function of prescribed medications: digoxin (top left), aspirin (top centre), beta blocker (top right), ACE-inhibitor (bottom left), loop diuretic (bottom centre) and NSAID (bottom right).

4.3.6.3 Outcome and LV function

LVSD, defined as an ejection fraction less than 35%, had a significantly lower survival rate compared to patients with ejection fractions above this. This was largely due LVSD having over twice the rate of cardiovascular death (figure 4.20).

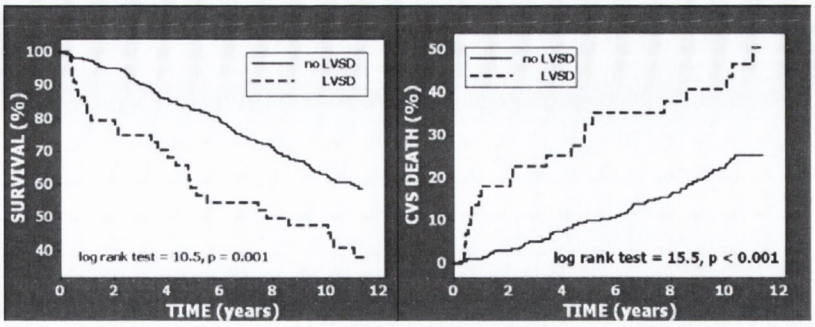

Figure 4.20 Kaplan-Meier curves of survival (left) and cardiovascular death (right) in those with and without LVSD.

As shown in Table 4.7, patients with LVSD had much higher proportion of deaths due to cardiovascular causes, with higher crude mortality rates of MI and HF. However, the proportion of cardiovascular deaths due to MI was the same in those with LVSD and those with normal LV function, but a higher proportion of CVS deaths in the LVSD group were due to HF (40.0 v 25.2%).

	No LVSD	LVSD
n	306	44
Crude mortality (%)	40.2	61.4
Cause of death (%)		
Cardiovascular	54.4	74.2
Cancer	21.1	7.3
Respiratory	11.4	3.8
Other	12.1	14.9
Crude mortality (%) due to:		
Myo Infarction	8.8	15.9
Heart Failure	5.6	18.2
CVA	5.6	2.3
Other	2.3	9.1
Proportion of CVS death (%)		
Myo Infarction	39.6	34.9
Heart Failure	25.2	40.0
CVA	25.2	5.1
Other	10.4	20.0

Table 4.7: Death coding comparing those with and without LVSD

Dividing the cohort based on BSE guidelines of LV impairment as per ejection fraction, there was a clear stepwise decrease in long term survival in patients with normal LV systolic function, mild LV impairment, moderate LV impairment and severe LV impairment. This was mirrored in the rate of cardiovascular death throughout the follow up period (Figure 4.21).

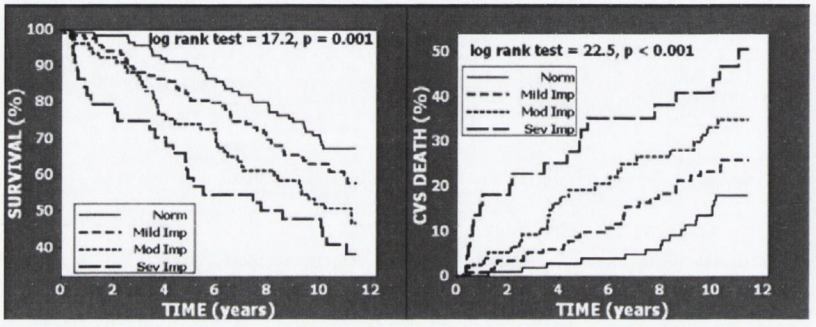

Figure 4.21 Kaplan-Meier curves of survival (left) and cardiovascular death (right) in the cohort as divided by BSE classification of LV systolic function

4.3.6.4 Outcome and Heart Failure

Compared to non-HF patients, patients with HF had poorer long term outcome in both all cause mortality and cardiovascular death (see figure 4.22).

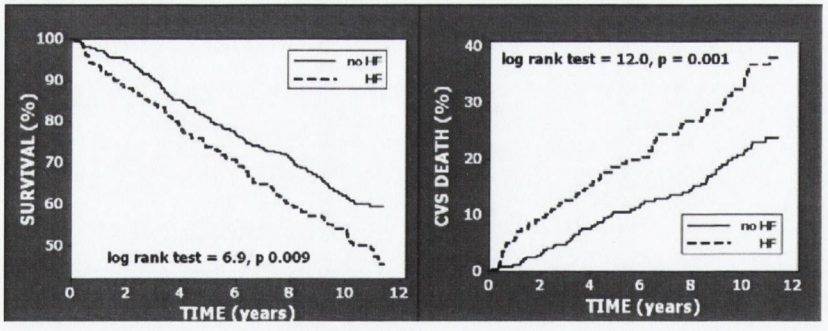

Figure 4.22 Kaplan-Meier curves of survival (left) and cardiovascular death (right) in those with and without heart failure

As shown in Table 4.8, patients with HF had a higher rate of deaths attributable to a cardiovascular death with higher crude mortality rates of MI and HF. The proportion of cardiovascular death in the HF group due to MI was similar to non-HF patients, but had a

higher proportion of cardiovascular deaths due to HF (34.3 v 19.6%). It is noteworthy that 4.0% of patients who did not have HF had deaths attributed to HF within the follow period.

	Non-HF	HF	HF-GP	HF-Hosp
n	301	199	97	102
Crude mortality (%)	40.2	51.7	42.2	60.7
Cause of death (%)				
Cardiovascular	50.4	65.0	56.1	71.0
Cancer	25.6	10.7	17.1	6.5
Respiratory	11.6	10.7	19.5	4.8
Other	12.4	13.6	7.3	17.7
Crude mortality (%) due to				
Myo Infarction	7.6	12.1	8.2	15.7
Heart Failure	4.0	11.5	9.3	13.7
CVA	5.3	5.0	4.1	5.9
Other	3.3	5.0	2.1	7.9
Proportion of CVS death (%)				
Myo Infarction	37.6	35.9	34.7	36.4
Heart Failure	19.6	34.3	39.2	31.8
CVA	26.1	14.9	17.5	13.6
Other	16.4	14.9	8.7	18.2

Table 4.8: Death coding comparing those with and without HF, and comparing HF-Hosp with HF-GP

Looking specifically at the HF patients we can see that for both all cause mortality and cardiovascular disease, HF-GP patients had a very similar outcome to non-HF patients, with HF-Hosp patients had significantly higher mortality (figure 4.23) than both of the other groups. As shown in table 4.8, the majority of deaths in the HF-Hosp cohort were due to a cardiovascular cause (71%), compared to just over half of deaths in the HF-GP group(56.1%). We can see that the HF-Hosp had higher crude rates of MI and HF deaths than HF-GP although the proportion of cardiovascular deaths due to MI, HF and stroke were similar between the groups.

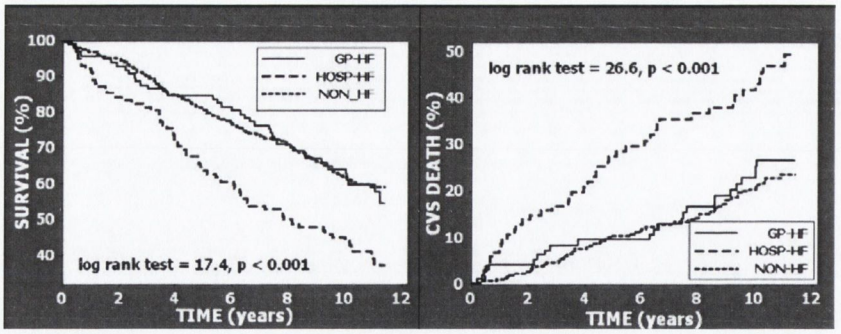

Figure 4.23 Kaplan-Meier curves of survival (left) and cardiovascular death (right) comparing non-HF, HF-Hosp and GP-HF patients.

NYHA class at screening proved to be an insensitive marker of long term outcome for the cohort as a whole (figure 4.24A). NYHA III had the lowest long term survival with NYHA II exhibiting the highest. NYHA class proved even less sensitive in patients with HF, with NHYA class IV actually having the best long term outcome (figure 4.24B).

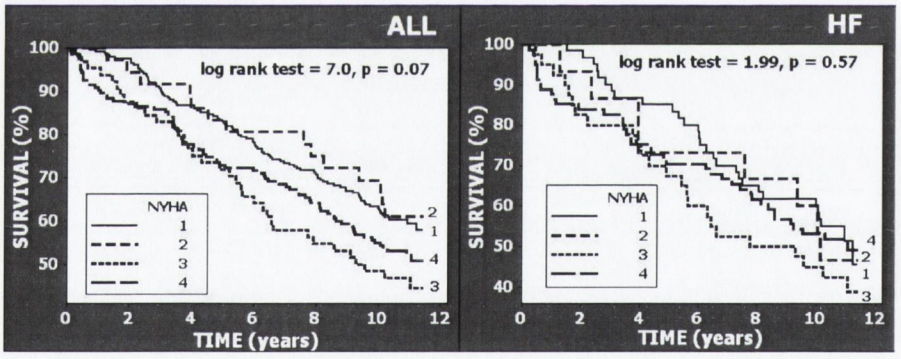

Figure 4.24 Kaplan-Meier curves of survival as per NYHA status in the entire cohort (A)) and in specifically in those with HF (B).

Looking specifically at cardiovascular death rate in the entire cohort, and specifically in HF patients, it was again demonstrated again that NHYA class at baseline did not accurately predict long term outcome (figure 4.25).

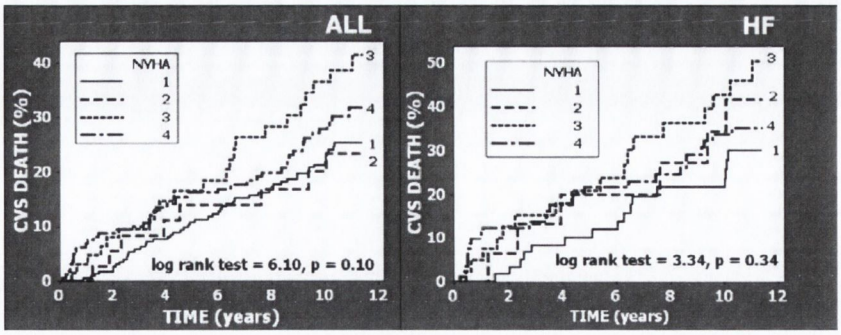

Figure 4.25 Kaplan-Meier curves of cumulative cardiovascular deaths per NYHA status in the entire cohort (A) and in specifically in those with HF(B).

4.3.6.5 Outcome: Cox regression

Table 4.9 shows univariate hazard ratios for all cause mortality and cardiovascular death for a variety of variables. Age and LVEF, both assessed as continuous variables, were univariate predictors of outcome. Male gender, LVSD, atrial fibrillation, previous MI, HF, digoxin and loop diuretic use were all strong predictors of all cause mortality and cardiovascular death. COPD also carried a significant univariate risk of poor outcome, although hypertension was significantly associated with good outcome. DM proved to be univariate predictor of all cause mortality but not of cardiovascular death.

	All cause mortality	p value	Cardiovascular death	p value
Age*	1.05 (1.03 – 1.06)	< 0.001	1.06 (1.04 – 1.08)	< 0.001
Male gender	1.55 (1.19 – 2.02)	0.001	1.70 (1.20 – 2.41)	0.003
Previous MI	1.71 (1.30 – 2.24)	< 0.001	1.92 (1.35 – 2.75)	< 0.001
Angina	0.98 (0.74 – 1.30)	0.87	1.06 (0.73 – 1.52)	0.77
Atrial fib	1.81 (1.82 – 2.48)	< 0.001	2.11 (1.42 – 3.16)	< 0.001
Hypertension	0.75 (0.58 – 0.97)	0.03	0.83 (0.48 – 0.96)	0.03
Diabetes Mellitus	1.50 (1.03 – 2.20)	0.03	1.34 (0.83 – 2.31)	0.21
COPD	1.77 (1.35 – 2.31)	< 0.001	1.70 (1.19 – 2.44)	0.004
LVEF*	0.97 (0.96 – 0.99)	< 0.001	0.96 (0.94 – 0.98)	< 0.001
LVSD	1.97 (1.30 – 2.98)	0.001	2.62 (1.59 – 4.32)	< 0.001
Heart Failure	1.42 (1.09 – 1.85)	0.009	1.83 (1.29 – 2.59)	0.001
ACE-Inhibitor	0.79 (0.60 – 1.05)	0.10	0.77 (0.53 – 1.12)	0.17
Beta-blocker	0.81 (0.56 – 1.19)	0.29	0.88 (0.54 – 1.43)	0.61
Loop diuretic	1.45 (1.10 – 1.91)	0.008	1.87 (1.29 – 2.74)	0.001
NSAID	1.11 (0.76 – 1.62)	0.60	1.44 (0.83 – 2.51)	0.20
Aspirin	1.29 (0.99 – 1.69)	0.06	1.30 (0.91 – 1.86)	0.147
Digoxin	2.17 (1.62 – 2.90)	< 0.001	2.57 (1.77 – 3.72)	< 0.001

Table 4.9: Univariate HRs for all cause mortality and cardiovascular death in the GP-Heart failure cohort

For multivariate analysis, all univariate predictors with a p value < 0.1 were included in the final model. As shown in table 4.10, age, LVEF, LVSD and male gender proved to be independent predictors of long term outcome in terms of all cause mortality. For cardiovascular death, only age, LVEF and LVSD proved to be independently predictive of outcome.

	All cause mortality	p value	Cardiovascular death	p value
Age*	1.04 (1.02 – 1.06)	**< 0.001**	1.05 (1.03 – 1.08)	**< 0.001**
Male gender	1.73 (1.18 – 2.50)	**0.004**	1.52 (0.95 – 2.45)	0.08
Previous MI	1.30 (0.84 – 2.00)	0.24	1.24 (0.73 – 2.08)	0.43
Atrial fib	0.84 (0.43 – 1.62)	0.60	1.36 (0.64 – 2.90)	0.425
Hypertension	1.01 (0.70 – 1.46)	0.96	0.94 (0.59 – 1.48)	0.78
Diabetes Mellitus	1.48 (0.85 – 2.60)	0.17	------	----
COPD	1.12 (0.77 – 1.64)	0.54	1.02 (0.63 – 1.66)	0.95
LVEF*	0.98 (0.96 – 1.00)	**0.02**	0.97 (0.95 – 0.99)	**0.002**
LVSD	1.73 (1.06 – 2.85)	**0.03**	2.34 (1.30 – 4.23)	**0.005**
Heart Failure	0.96 (0.61 – 1.52)	0.87	0.94 (0.53 – 1.67)	1.67
ACE-Inhibitor	0.89 (0.58 – 1.40)	0.58	------	----
Loop diuretic	1.07 (0.68 – 1.70)	0.78	1.25 (0.68 – 2.27)	0.46
Aspirin	0.89 (0.59 – 1.34)	0.58	------	----
Digoxin	1.76 (0.98 – 3.20)	0.06	1.63 (0.81 – 3.26)	0.17

Table 4.10: Multivariate HR for all cause mortality and cardiovascular death in GP-Heart Failure cohort

4.3.5.6 Outcome and Natriuretic peptides

The natriuretic peptides proved to be prognostic of long term outcome. LogNT-ANP, assesses as a continuous variable, was a strong univariate predictor of all cause mortality [HR 1.48 (1.24 – 1.76), p < 0.001] and of cardiovascular death [HR 1.84 (1.46 – 2.32), p < 0.001]; however, logNT-ANP proved not to be an independent predictor of outcome following multivariate analysis, with adjusted HRs of 1.16 (0.86- 1.57) and 1.15 (0.76 – 1.73) respectively for all cause mortality and cardiovascular death respectively.

LogBNP was also predictive of outcome and had very similar unadjusted HRs to logNT-ANP [all cause mortality 1.55 (1.32 – 1.82), cardiovascular death 1.89 (1.54 – 2.32)]. However,

unlike logNT-ANP, log BNP remained an independent predictor of adverse outcome with an adjusted HR of 1.49 (1.13 – 1.97), p =0.005 for all cause mortality and 1.46 (1.02 – 2.10), p = 0.041 for cardiovascular death. A BNP of greater than 50pg/ml carried unadjusted HRs of 2.0 (1.53 – 2.67) for all cause mortality and 2.9 (2.00 -4.31) for cardiovascular death, compared to a BNP of less than this. These HRs increased to 2.3 (1.74 – 3.06) and 3.3 (2.3 – 4.8) respectively when a cut-off of 100pg/ml was used.

The entire cohort was divided into quartiles based on BNP concentration. Figure 4.26 shows Kaplan-Meier curves for survival and cardiovascular death throughout the follow up period (quartile 1 = lowest BNP). Quartile 4 had less than half the survival of quartile 1, and over five times as many cardiovascular deaths. Quartiles 2 and 3 had largely similar outcomes but quartile 3 did have a higher rate of cardiovascular death than quartile 2.

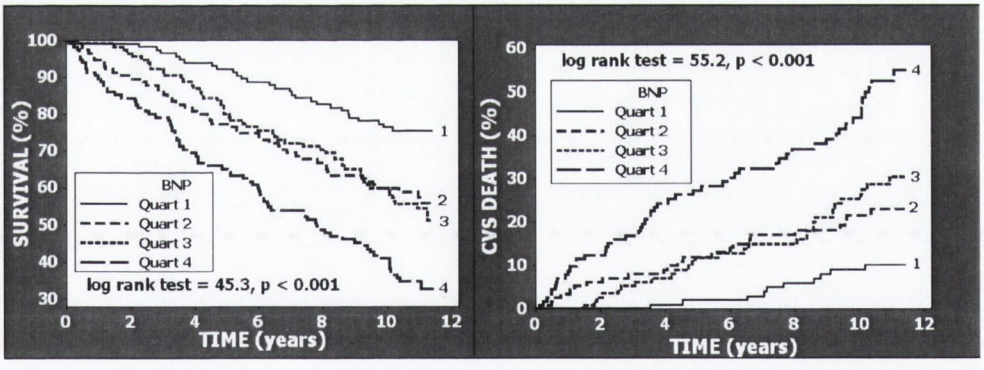

Figure 4.26 Kaplan-Meier curves of survival (left) and cardiovascular death (right) per BNP quartile.

Unadjusted and adjusted HRs for the BNP quartiles, using quartile 1 as reference, are detailed in table 4.11. Having a BNP in the fourth quartile carried an adjusted risk of death of two and a half times that of a BNP in the lowest quartile, and over three times an adjusted risk of cardiovascular death.

	All cause mortality				Cardiovascular death			
	Unadjusted	p	Adjusted	p	Unadjusted	p	Adjusted	p
Quart 1	1.0	-	1.0	-	1.0	-	1.0	-
Quart 2	2.04 (1.28 – 3.25)	0.003	1.73 (0.93 – 3.23)	0.09	2.69 (1.28 – 5.64)	0.009	1.77 (0.68 – 4.55)	0.24
Quart 3	2.12 (1.34 – 3.35)	0.001	1.24 (0.65 – 2.38)	0.52	3.38 (1.65 – 6.91)	0.001	1.54 (0.59 – 4.00)	0.38
Quart4	3.90 (7.52 – 6.02)	0.001	2.49 (1.28 – 4.85)	0.007	7.65 (3.88 – 15.1)	0.001	3.15 (1.21 – 8.21)	0.019

Table 4.11: Univariate and multivariate HRs for all cause mortality and cardiovascular death per BNP quartile.

4.3.5.7 Outcome and Renal function

Poorer renal function was associated with poorer long term outcome.

eGFR

Crude mortality rates increased as eGFR declined; this trend was even more marked with the cardiovascular death rate (see figure 4.27).

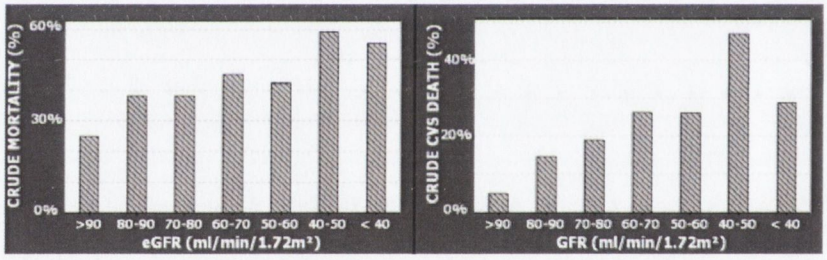

Figure 4.27: Barcharts indicating crude mortality (left) and crude cardiovascular deaths (right) in cohort divided into 10ml/min/1.73m² eGFR increments

eGFR, assessed as a continuous variable, was a univariate predictor of outcome with unadjusted HRs of 0.986 (0.978 -0.995) for all cause mortality and 0.978 (0.967 – 0.989) for cardiovascular death. However, following multivariate analysis, it proved not to be a independent predictor of outcome, although there was a trend toward statistical significance; adjusted HRs for all cause mortality and cardiovascular death were 0.988 (0.974 – 1.002), p = 0.088 and 0.984 (0.963 – 1.002), p = 0.084 respectively.

Having an eGFR of less than 60 ml/min/1.73m² carried a poorer prognosis compared to having an eGFR above this, as illustrated in figure 4.28.

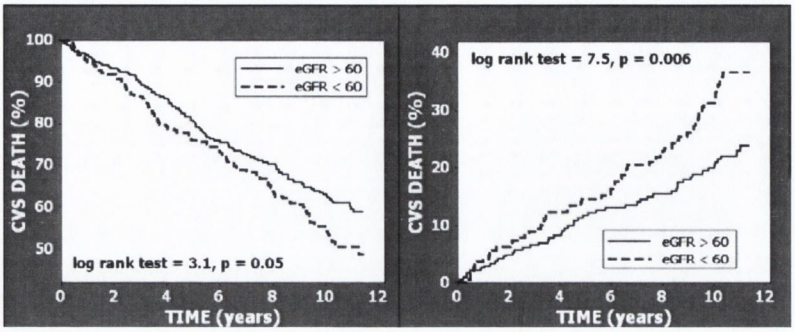

Figure 4.28 Kaplan-Meier curves of survival (left) and cardiovascular death (right) comparing eGFR > 60ml/min/1.73m² to eGFR < 60ml/min/1.73m²

Compared to an eGFR > 60ml/min/1.73m², having an eGFR of less than this had unadjusted and adjusted HRs of 1.32 (0.99 – 1.74) and 1.39 (0.94 – 2.07) respectively for all cause mortality. Corresponding values for cardiovascular death were 1.67 (1.15 – 2.42) and 1.50 (0.89 – 2.52).

Dividing the cohort into quartiles based on eGFR, we can see that quartile 1 (with the highest eGFR) had the best long term survival and lowest rate of cardiovascular deaths, with quartile 4 having the worst outcome; this is illustrated in figure 4.29.

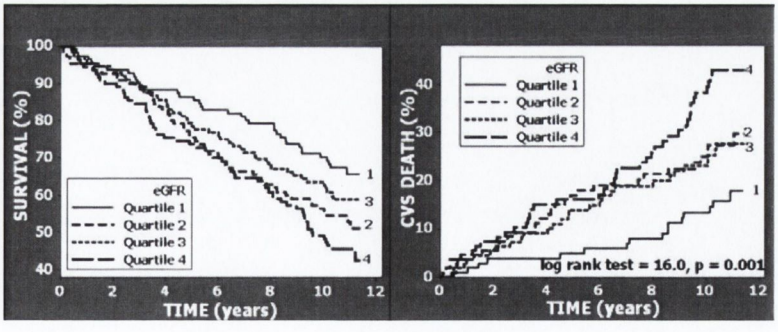

Figure 4.29 Kaplan-Meier curves of survival (left) and cardiovascular death (right) comparing eGFR quartiles.

Quartiles 2 and 3 had very similar mortality rates, particularly with regard to cardiovascular deaths. eGFR quartiles were univariate predictors of outcome, as shown in table 4.12. Following multivariate analysis, we can see that, compared to quartile 1, quartile 4 was an independent predictor of cardiovascular death [adjusted HR = 2.35 (1.04 – 5.34), p =0.041] and almost an independent predictor of all cause survival [adjusted HR = 1.79 (0.98 – 3.25), p = 0.06].

	All cause mortality		**Cardiovascular mortality**	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Quartile 1	1.0	1.0	1.0	1.0
Quartile2	1.58 (1.04 – 2.41)	0.96 (0.52 – 1.77)	1.98 (1.07 – 3.66)	1.13 (0.49 – 2.61)
Quartile 3	1.32 (0.86 – 2.04)	1.07 (0.59 – 1.95)	1.86 (1.01 – 3.43)	1.28 (0.56 – 2.91)
Quartile 4	1.92 (1.28 – 2.89)	1.79 (0.98 – 3.25)[a]	3.00 (1.68 – 5.35)	2.35 (1.04 – 5.34)†

Table 4.12: Univariate and multivariate HRs for all cause mortality and cardiovascular death based on eGFR quartile ([a] p =0.057 † p = 0.041)

Examining the death coding of the cohort when divided based on CKD status reveals a definite trend (table 4.13). As renal function deteriorates, overall mortality increases, with a higher proportion of deaths being due to a cardiovascular cause. However, this seems to be largely due to HF deaths, given that the crude mortality of deaths due to MI was not different between CKD stage 2, 3 or 4; rather, the rate of HF deaths increases dramatically as renal function deteriorates, with a much higher proportion of cardiovascular deaths being due to HF.

Using CKD stage 1 as reference, CKD stages 2, 3 and 4 carried univariate HRs of 1.78 (0.72 – 2.37), 2.16 (0.88 – 5.33) and 4.02 (1.31 – 12.3) respectively for all cause mortality and 4.72 (0.65 – 34), 7.10 (0.98 – 51) and 12.4 (1.45 – 106) for cardiovascular death. Following

multivariate analysis, CKD stages proved not to be independent predictors of outcome: adjusted HRs for all cause mortality, eGFR 60-90 [0.7 (0.27 – 1.84), p = 0.47], stage 3 [0.97 (0.37 – 2.61), p = 0.96] and stage 4 [2.05 (0.54 – 7.7), p =0.29]; adjusted HRs for cardiovascular death, eGFR 60-90 [1.58 (0.21 – 12.0), p = 0.66], stage 3 [2.30 (0.29 – 17.9), p = 0.43] and stage 4 [4.39, (0.41 – 46.0), p =0.22].

	eGFR			
	> 90	**60 - 90**	**CKD stage 3**	**CKD stage 4**
n	20	229	180	13
Crude mortality (%)	25.0	41.5	48.9	61.5
Cause of deaths (%)				
Cardiovascular	20.0	52.5	64.9	62.6
Cancer	60.0	24.1	11.5	12.5
Respiratory	20.0	10.6	10.2	12.5
Other	0	12.5	13.7	12.5
Crude mortality (%) due to				
Myo Infarction	0.0	8.7	10.0	7.7
Heart Failure	5.0	4.4	10.0	23.1
CVA	0.0	4.8	7.2	0.0
Other	0.0	3.9	5.7	7.7
Proportion of CVS death (%)				
Myo Infarction	0	39.9	31.5	20.0
Heart Failure	100	20.2	31.5	60.0
CVA	0	22.0	22.7	0
Other	0	17.9	17.9	20.0

Table 4.13: Death coding comparing CKD status

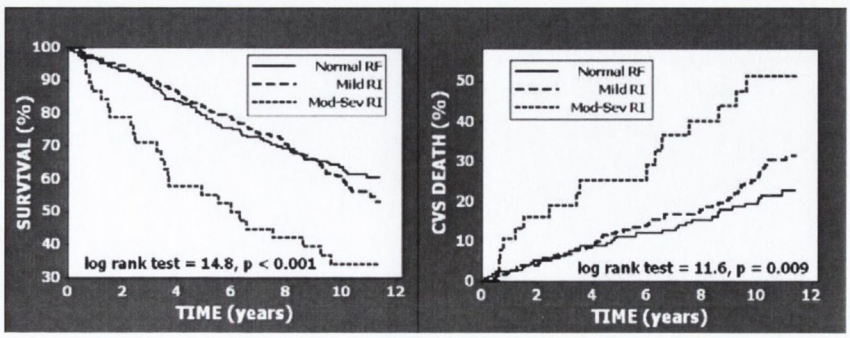

Figure 4.30 Kaplan-Meier curves of survival (left) and cardiovascular death (right) based on renal function as based on creatinine concentration.

Creatinine

As shown in figure 4.30, those with normal renal function and those with mild RI had a very similar survival rate although those with mild RI did have an increased rate of cardiovascular deaths. Moderate-severe RI had a much higher mortality than both the other groups; univariate HR are shown in table 4.14. Following multivariate analysis, moderate-severe RI proved to be an independent predictor of all cause mortality, although not of cardiovascular disease ($p = 0.12$).

	All cause mortality		**Cardiovascular mortality**	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
Normal renal function	1.0	1.0	1.0	1.0
Mild RI	1.13 (0.84 – 1.54)	0.91 (0.58 – 1.45)	1.40 (0.92 – 2.11)	1.05 (0.57 – 1.94
Mod-severe RI	2.36 (1.49 – 3.73)	2.25 (1.16 – 4.35)	3.02 (1.67 – 5.47)	2.01 (0.83 – 4.88

Table 4.15: Univariate and multivariate HRs for all cause mortality and cardiovascular death based on renal function as defined by creatinine concentration [RI, renal impairment]

Table 4.15 shows the rate and cause of death of the cohort when divided based on renal impairment, as defined by creatinine. A similar pattern as with CKD classification is seen, whereby the proportion of deaths due to cardiovascular disease increases as renal function falls. Again, this seems to be largely due to an excess of deaths attributed to HF.

	Creatinine		
	Normal	Mild RI	Mod-sev RI
n	179	225	38
Crude mortality (%)	39.1	44.9	65.8
Cause of deaths (%)			
Cardiovascular	50.1	61.5	64.0
Cancer	24.3	17.8	8.1
Respiratory	14.3	8.9	8.1
Other	11.5	11.8	20.0
Crude mortality (%) due to			
Myo Infarction	6.1	11.6	5.3
Heart Failure	5.0	7.0	18.4
CVA	5.0	5.8	5.3
Other	3.4	3.1	8.4
Proportion of CVS death (%)			
Myo Infarction	31.1	42.0	12.6
Heart Failure	25.5	25.3	43.8
CVA	25.5	21.0	12.5
Other	17.3	11.3	20.0

Table 4.15: Death coding comparing renal function as defined by creatinine.

4.3.6.7 Outcome: Influence of Heart Failure and Renal Failure

The cohort was divided based on the presence or absence of HF, and further by the presence or absence of CKD (defined for this purpose as < 60ml/min/1.73m^2). Thus there were four groups; those without HF or CKD (HF-CKD-); those with CKD but no HF (HF-CKD+); those with HF but normal renal function (HF+CKD-) and; those with both HF and CKD (HF+CKD+). The baseline characteristics of these four sub-groups are shown in table 4.16

The HF+CKD+ patients were much older than the other groups, and had a mean age of almost ten tears older than HF-CKD- patients. The proportion of males in the HF-CKD+ and HF+CKD+ groups was low. Compared to HF-CKD-, the rate of established cardiovascular

disease was higher in the HF-CKD+ patients, and higher again in HF+CKD- and HF+CKD+ groups. COPD was much less prevalent in the HF-CKD- group than in the other groups.

	HF – CKD -	HF - CKD +	HF+ CKD -	HF + CKD +	p value
n	176	98	73	95	
Age (years)	63.4 ± 12.5	71.5 ± 9.7	69.4 ± 10.0	73.0 ± 9.2	< 0.001
Male (%)	40.3	24.5	43.8	26.3	0.005
BMI (kg/m²)	28.2 ± 5.8	27.2 ± 4.7	28.2 ± 5.7	27.8 ± 5.4	0.46
Obese (%)	37.5	25.5	30.1	27.4	0.25
Systolic BP (mmHG)	150.4 ± 26.5	151.2 ± 26.0	142.9 ± 26.6	140.8 ± 26.0	0.007
Diastolic BP (mmHG)	83.3 ± 13.0	77.9 ± 13.2	79.8 ± 15.5	73.2 ± 15.3	< 0.001
Myo Infarction (%)	17.6	27.6	39.7	41.1	< 0.001
Angina (%)	21.6	27.6	45.2	50.5	< 0.001
Atrial Fibrillation (%)	9.1	13.3	24.7	20.0	0.006
NYHA (%)					
I	56.3	56.1	31.5	31.6	< 0.001
II	6.8	8.2	4.1	8.4	
III	10.2	5.1	28.8	15.8	
IV	25.6	30.6	35.6	42.1	
Hypertension (%)	63.6	59.2	39.7	53.7	0.006
Diabetes Mellitus (%)	10.8	9.2	9.6	14.7	0.59
Asthma (%)	11.9	11.2	11.0	15.8	0.71
Arthritis (%)	41.5	60.2	50.7	54.7	0.016
COPD (%)	26.1	40.8	39.7	43.2	0.006
LVEF	50.3 ± 10.0	51.4 ± 9.7	45.4 ± 12.1	45.8 ± 12.3	0.001
LVSD	5.1	3.1	13.7	16.8	< 0.001
BNP	22.6 (42.6)	52.0 (87.2)	63.6 (96.0)	67.6 (148.8)	< 0.001
NTANP	3.8 (4.1)	7.8 (7.4)	5.6 (5.6)	7.8 (10.2)	< 0.001
Medications (%)					
Loop diuretic	28.4	48.0	93.2	90.5	< 0.001
Any diuretic	46.6	64.3	93.2	93.7	< 0.001
ACE-Inhibitor	42.6	28.6	34.2	32.6	0.08
Beta blocker	14.2	21.4	11.0	16.8	0.26
Digoxin	10.8	14.3	31.5	26.3	< 0.001
Aspirin	24.4	30.6	45.2	48.4	< 0.001
NSAID	13.1	17.3	16.4	14.7	0.82

Table 4.16: Baseline characteristics of cohort as divide by presence or absence of CKD and/or HF.

Natriuretic peptides were relatively low in the HF-CKD- group, but the other three groups had very similar concentrations of both BNP and NT-ANP. ACE-inhibitors were more often prescribed in the HF-CKD- group. Loop diuretic use was twice as high in the HF-CKD+ patients than in the HF-CKD-, and almost four times higher in the HF+CKD+ patients.

Long term outcome of the four sub-groups are shown in figure 4.31. HF+CKD+ had the worst prognosis, with HF-CKD- having the best outcome. Notably, patients with HF alone had a very similar outcome to patients with CKD alone. Compared to HF-CKD- patients, univariate HRs for all cause mortality in HF-CKD+ patients, HF+CKD+ patients and HF+CKD+ patients were 1.14 (0.78 – 1.66), 1.10 (0.72 1.69) and 1.60 (1.12 – 2.29) respectively. Corresponding univariate HRs for cardiovascular death were 1.7 (1.02 – 2.84), 1.71 (0.98 – 2.99) and 2.38 (1.45 – 3.89).

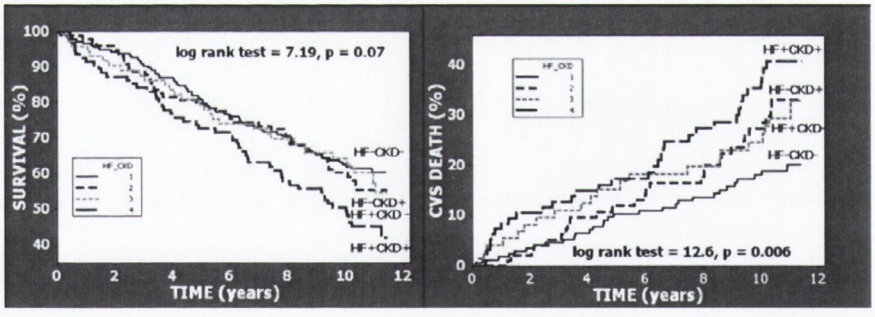

Figure 4.31 Kaplan-Meier curves of survival (left) and cardiovascular death (right) of cohort as divided by presence or absence of CKD and/or HF.

Table 4.17 reveals the cause of deaths in the four sub-groups. In patients without HF, those with CKD had a higher rate of cardiovascular death (65.1% v 43.4 %,), but this difference was not mirrored in patients with HF. Patients with CKD alone and HF alone had very similar profiles in terms of cause of death, crude mortality rates due to HF and MI and proportion of CVS deaths attributed to different cause. The crude mortality due to MI was similar in those with CKD alone, HF alone and with both HF and CKD. CKD appears to be

associated with an increased risk of death due to HF irrespective of whether HF was present or not at screening; in those without HF at baseline, the crude mortality due to HF was higher in those with CKD than in those without (6.1% v 3.4%). However, in those who did have HF at baseline, those with CKD were over twice as likely to die from HF as those without CKD (15.8% v 6.8%, p = 0.05). The presence of CKD with HF led to increased overall mortality, largely due to an excess of deaths due to HF.

	Renal Function/HF status			
	CKD- HF -	CKD+ HF -	CKD- HF +	CKD+ HF+
n	176	98	73	95
Crude mortality (%)	39.2	43.9	42.5	55.8
Cause of death (%)				
Cardiovascular	43.4	65.1	67.7	64.1
Cancer	30.3	16.2	16	7.5
Respiratory	14.5	7.1	3.4	13.3
Other	11.5	11.6	12.9	15.0
Crude mortality (%) due to				
Myo Infarction	6.8	10.2	11.1	9.5
Heart Failure	3.4	6.1	6.8	15.8
CVA	3.4	8.2	6.8	5.3
Other	3.4	4.1	4.1	5.3
Proportion of CVS death (%)				
Myo Infarction	40.0	35.7	38.5	26.5
Heart Failure	20.0	21.3	23.6	44.1
CVA	20.0	28.7	23.6	14.7
Other	20.0	14.4	14.3	14.7

Table 4.17: Death coding of cohort as divided by presence or absence of CKD and/or HF

4.4 Discussion

The first thing to acknowledge is the slightly unusual nature of this cohort. This is not a group of individuals with HF, and as such can not be directly compared with other HF studies that have addressed renal function and outcome. Rather, this is a selection of patients from primary care taking HF therapies such as digoxin, ACE-inhibitors or diuretics, *some* of which had HF. Using this inclusion criteria, it would be expected that patients with asymptomatic atrial fibrillation (digoxin), hypertension (diuretic, ACE-inhibitor) or fluid retention due to lung, liver or renal disease (diuretics) might be included in the cohort.

It is certainly unlikely that these entry criteria would lead to recruitment of healthy individuals and this proved to be the case. This was an elderly cohort (mean age 68.5 ± 11.6 years) with a large number of co-morbidities; 40% had HF, with a similar proportion having arthritis or chronic lung disease. 60% had hypertension and over one in ten had DM. The prevalence of AF and LVSD was between 10-15% and approximately one third of individuals has angina or previously sustained a MI. One half of the cohort reported breathlessness, with over one third of individuals reporting breathlessness at rest or on minimal exertion (NHYA class 4).

The poor co-morbidity profile is manifest when mortality is assessed. Almost one half of the cohort died during the follow up period, with mean mortality rate of approximately 4% per year. Although high, this mortality rate is still lower than that seen in most chronic HF studies where annual death rates of 4.3% (87) and 5.5% (47) are quoted in observational studies; drug therapy trials in HF of enalapril (85) and candesartan (46) reported annual mortality rate

of 8.1% and 7.6% respectively, whilst studies incorporating those with NYHA class 3 and above had death rates of 10% per year (242), and even as high as 20% (162).

Within the cohort as a whole, patients with HF had the worst co-morbidity profile, being older by a mean of 5 years and having a much higher prevalence of angina, AF and previous MI. NYHA class was significantly worse in HF patients, although it is noteworthy that over one quarter of patients without HF had NHYA class IV breathlessness. The prevalence of non cardiovascular co-morbidities was similar between HF and non-HF patients, with the exception of COPD which was more common in the HF group. Within those individuals with HF, the HF-Hosp group were older, more likely to be male and had a worse cardiovascular profile and NYHA status (Table 4.2). A similar pattern was seen in ECHO findings within the cohort, whereby HF patients had higher rates of LVSD, LVH, dilated LV and valvular disease (table 4.3). Again, within the HF sub-cohort, HF-Hosp had a worse profile thanHF-GP.

Drug therapy reflects clinical practice in 1995, which was also manifest in the post-MI cohort in chapter 2. At this time, ACE-inhibitor therapy for HF/LVSD was beginning to become widespread practice; however, beta-blocker therapy in HF was still considered a contra-indication. This is apparent in the HF-Hosp group with its high rates of LVSD, dilated LV and previous MI; over half were taking an ACE-inhibitor at the time of screening compared to 6.7% taking beta-blockers. Spironolactone use was very low, but the RALES study showing its benefit in NYHA class 3 HF was published in 1999 (162).

Given that this was an elderly cohort, with multiple co-morbidities and high diuretic usage, it's not a surprise to find a high rate of renal impairment. 43.6% of the group had an eGFR of less than 60ml/min/1.73m^2- this is comparable to HF studies assessing renal function and outcome where the rate of CKD stage 3 or worse varies from 33 to 57% (46-48,90). Only 8.6% of the cohort had creatinine levels above 1.5 mg/dl (132.6 μmol/l) and thus fulfilled criteria for moderate to sever renal impairment, although over half the cohort had mild renal impairment based on having a creatinine between 88.4 and 132.6μmol/l.

eGFR was significantly worse in patients with HF, and tended to be worse in LVSD. However, eGFR and creatinine didn't perform well at identifying these individuals from the cohort using ROC analysis although it is noteworthy that the natriuretic peptides did not fare much better.

There were a relatively large number of univariate predictors of outcome in this cohort. As expected, age, LVSD, male gender and DM all proved prognostic of adverse outcome. Hypertension actually predicted good outcome for both all cause mortality and cardiovascular disease; indeed, hypertensives actually also had better renal function than normotensives. These apparent anomalies can be explained by re-examining the cohort. Given ACE-inhibitor use was an inclusion criterion, the cohort will thus include patients with HF, but also patients on ACE-inhibitors for essential hypertension; the same might be true for diuretics such as bendrofluazide. Thus, analysis of this cohort will result in comparing relatively young patients with hypertension with elderly HF patients; it is therefore not a surprise to see hypertensive patients having a relatively better outcome.

HF-Hosp patients had by far the worst outcome with a crude mortality rate of almost 60% during the follow up period. HF-GP and non-HF patients had remarkably similar outcomes, even though HF-GP patients were older, and had higher rates of cardiovascular disease, and a lower eGFR. This may be explained by the non-HF patients having proportionally more males and higher rates of hypertension; however, it certainly confirms that even in the absence of HF, this was a particularly unhealthy cohort.

eGFR, assessed as a continuous variable, and CKD status were both univariate predictors of all cause mortality and cardiovascular outcome, but failed to remain independent predictors after multivariate analysis. However, dividing the cohort into quartiles did reveal that the quartile with the lowest eGFR was independently predictive of cardiovascular death and almost predictive of all cause mortality ($p = 0.057$), with impressive HRs. Most of the HF studies that have assessed eGFR and outcome did find eGFR to be an independent predictor of outcome (46,47,89,90), but as already discussed, this is not a cohort of HF patients. However, the hypotheses regarding renal function and prognosis in HF could still apply to this cohort, that is, an elderly group with high rates of established cardiovascular disease.

Moderate to severe renal impairment as defined by serum creatinine also proved to be independently predictive of all cause mortality and cardiovascular death. Regardless of whether eGFR or serum creatinine was used, it is apparent that renal impairment was associated with increased rate of cardiovascular deaths, and particularly with death due to HF. This may well be related to impaired renal excretion of sodium and fluid, thus exacerbating HF symptoms.

Dividing the cohort based on the presence or absence of HF and/or CKD revealed further interesting results (Table 4.16). Those individuals without HF and with normal renal function unsurprisingly had the best prognosis; however, even in the absence of these, one third of individuals died. Patients with CKD alone and those with HF alone had very similar outcomes with almost identical distributions of death coding; this is despite the CKD alone group, although admittedly older, having a lower rate of females, cardiovascular disease and one quarter the prevalence of LVSD. Much capital and time has been invested in developing methods of identifying HF in the community via screening projects including natriuretic peptides and echocardiography when a simple creatinine assessment can actually reveal patients in the community with equally as bad a prognosis as HF. As would be expected, the composite of HF and CKD carried the worst prognosis of all, with a particularly high rate of deaths attributed to HF.

The relationship between lower renal function and elevated natriuretic peptides has again been confirmed in this study. BNP and NT-ANP surprisingly did not perform much better than eGFR or serum creatinine in identifying HF or LVSD from the cohort, although recent evidence suggests that natriuretic peptides are not performing as well as might be hoped as screening tools (213-215). Unlike other evidence (209), there was no relationship between NYHA class and BNP levels, even in those patients with HF. However, BNP has again proven to be an excellent prognostic marker, identifying individuals in this heterogeneous cohort at risk of premature death, and particularly cardiovascular death.

4.4.1 Limitations

This study might have been improved by gathering more information regarding medical history and renal function. There were a large number of patients with previous MI and information on timing, extent and treatment of MI, plus any subsequent revascularisation would have been of benefit. Equally, more information on the severity of HF (such as hospitalisations, peripheral oedema etc) might have helped risk stratifying these individuals. Urinanalysis, particularly looking for proteinuria, would have allowed further exploration of the association between renal function and outcome

This screening visit for this study took place over 12 years ago. Since this time, large improvement in the treatment of HF, DM, MI and HF/LVSD have been made; a similar cohort study performed in 2009 is likely to yield a very different drug profile. As such, it is difficult to apply the findings of this study to the modern population.

Smoking and dyslipidaemia are both recognised as factors influencing adverse cardiovascular outcome. This study was limited in that lipid analysis was not performed on this cohort and reliable smoking data was not available.

Death coding based on information from the death certificate depends very much on who completed the certificate. As such, sub-dividing deaths into cardiovascular and subsequently to type of cardiovascular death may not be accurate. Information on hospital admission and any further adverse cardiovascular events during the follow up period would have allowed analysis of renal function on cardiovascular morbidity.

4.4.2 Conclusion

This cohort of patients represented an elderly group of Glaswegians with a large number of co-morbidities and poor exercise tolerance. Established cardiovascular disease was common, as were other illnesses such as obstructive lung disease and arthritis. In this heterogeneous group, renal impairment was very common, with almost one half having stage 3 CKD or worse.

Renal function proved to be an independent predictor of adverse outcome. Moderate to severe renal impairment as defined by serum creatinine carried an adjusted increased risk of 125% and 101% for all cause mortality and cardiovascular death respectively, compared to individuals with normal serum creatinine. CKD classification did not independently predict outcome; however, the lowest eGFR quartile (compared to the highest quartile) was independently predictive of cardiovascular death with an adjusted HR of 2.35, and there was as strong trend toward independently predicting all cause mortality (HR = 1.79, p = 0.057).

In this elderly cohort, the presence of CKD (eGFR < 60ml/min/1.73 m^2) without HF carried a remarkably similar prognosis to patients with HF and normal renal function. It appears that renal impairment was particularly associated with death due to HF. A strong association between renal function and natriuretic peptides was demonstrated. Renal function and natriuretic peptides performed comparably at identifying HF patients and LVSD from the cohort. BNP levels were strongly predictive of adverse outcome, particularly cardiovascular death.

CHAPTER 5

MONICA (GENERAL POPUALTION) COHORT

5.1 Introduction

CKD is becoming increasingly prevalent throughout the Western world. Perhaps up to 5% of the population aged over 20 years will have an eGFR < 60ml/min/1.73m^2, with the proportion reaching almost 12% in those aged over 65 years (29-31). This is predicted to become increasingly common as the population ages, and it is thought that atherosclerotic disease is becoming increasingly culpable (27,32,33). It's unequivocal that severe RF is associated with poor prognosis, particularly with cardiovascular disease; however, it is now becoming apparent that even milder forms of renal impairment are independently predictive of adverse outcome within the general population (67-72,75,118).

Its worth noting that the earliest studies assessing less severe renal impairment and outcome in the general population disagreed regarding whether there was independent association with all cause mortality (67,69,93). Culleton et al (67) concluded that mild renal impairment was predictive of all cause mortality in men but not women, whilst Garg et al (93) found no independent association in either gender; this countered the conclusion from Fried et al (69) in 1998 that a raised creatinine was independently associated with adverse outcome. The adoption of the MDRD formula and eGFR coincided with a number of studies concluding that milder forms of renal impairment was indeed predictive of all cause mortality (71,243), although this has again been questioned as recently as 2006 (68). There is less discussion regarding the association between mild renal disease and cardiovascular disease, as reduced eGFR has been shown to predict cardiovascular death (68,70,72) premature cardiovascular disease, MI(74,75) and other major adverse cardiovascular events (118).

The Glasgow MONICA study from 1992 has generated a number of publications, with a particular interest in LV function, asymptomatic and symptomatic LVSD and the diagnostic strength of BNP in the general population (4,210,211,230). Renal function has never been assessed in this population; furthermore, long term outcome has not been examined, although one study did report mortality data for up to 4 years.

No stored serum samples were available from the original 1992 cohort study, although samples were available from the 1995 rescreen. In this section, the prevalence of renal disease in a cohort of the general population from Glasgow will be calculated, as will its influence on long term mortality. The association between cardiovascular risk factors, echo data, symptoms and BNP and renal function will also be studied.

5.2 Methods

5.2.1 Patient identification

As detailed elsewhere (4), 2000 people (200 men, 200 women, in each 10-year age band from 25 to 74 years) who had attended the third Glasgow MONICA coronary-risk-factor survey (9) were invited to take part in this study in 1992; 1640 patients attended for a screening visit as detailed below.

In 1996 these same individuals were again invited to attend on a third occasion. A similar screening process as detailed below was performed. On this occasion, eight hundred and fifty-one people attended.

5.2.2 Screening Visit

Questionnaire

All participants completed a questionnaire on demography, current medication, and a history of myocardial infarction, angina, or diabetes mellitus, and answered the Medical Research Council questions on breathlessness (234).

Echocardiography

Standard two-dimensional echocardiography (Acuson 128) was carried out with the participant reclining at 40°, in the left lateral position. Images were stored on videotape and analysed on-line. The left-ventricular ejection fraction was calculated by the biplane disc summation method (Simpson's rule) (235). Each ejection fraction is a mean of three cardiac cycles. Echocardiograms were deemed of acceptable quality if 80% or more of the endocardium was visible.

Blood pressure

Blood pressure was taken as a mean of two readings, measured with the participant seated (after 5 min rest), on the right arm, with a random zero sphygmomanometer. Serum cholesterol was recorded as the average of two measurements.

Blood sampling

Blood samples were taken from the antecubital fossa. Analysis for blood glucose, and cholesterol were performed. Serum samples were frozen at time of screening. Samples from the rescreen in 1995 were subsequently thawed in October 2006 and immediately analysed for creatinine concentration on an Abbott c8000 analyser using a reaction rate Jaffe method

(Abbott Diagnostics, US). Serum creatinine levels have been shown to remain stable when samples are stored at very low temperatures for many years (245). Estimated glomerular filtration rate (eGFR) was then calculated for each individual using the Modified Diet in Renal Disease formula [186 x [SerumCreatinine (μmol/L) x 0.0113]$^{-1.154}$ x Age (years)$^{-0.203}$ (x 0.742 if female)].

5.2.3 Definitions

The definitions used in this study were as follows:

Ischaemic heart disease (IHD) was a history of angina (self reported or use of nitrates); a history of myocardial infarction; or ECG evidence of ischaemia or infarction.

Hypertension was a measured blood pressure of more than 140 mm Hg systolic, more than 90 mm Hg diastolic, or both; current treatment with antihypertensive medication; or both blood pressure above the cutoffs and current treatment.

Diabetes mellitus was a history of diabetes, current treatment with an oral hypoglycaemic agent or insulin, or both characteristics.

Left-ventricular systolic dysfunction was defined as LVEF of less than 35%

Renal impairment was defined using both eGFR and serum creatinine. With eGFR, current guidelines regarding CKD classification were used(24); For CKD stage 1 and 2, guidelines indicate that there must be evidence of kidney damage in the form of proteinuria or haematuria; urinalysis was not available to us and thus we classified patients as CKD stage 1

or 2 based solely on their calculated eGFR. All patients with eGFR < 60ml/min/1.73m^2 were classified as CKD stage 3 or worse (CKD 3+), even if they fulfilled criteria for CKD stage 4 or 5. All individuals with eGFR >90ml/min/1.73m^2 were classified as CKD stage 1 or better (CKD 1-).

Three different definitions of renal impairment using serum creatinine were used. The first used cut-offs derived from previous NHANES analysis (93); men with serum creatinine less than 122μmol/l and women with creatinine less than 104μmol/l were said to have normal renal function, with those above this level having "NHANES renal impairment (RI). The second definition used was from Framingham data (67), and men with creatinine >136Umol/l and women >120Umol/l were said to have "Framingham RI". The final method for defining renal impairment was designed from the MONICA cohort, using previously described techniques (244). From the MONICA cohort, a healthy reference sample of individuals who were free of hypertension, diabetes mellitus, left ventricular dysfunction, angina and previous MI at the original 1992 screening were selected. From these, normal sex-specific 95th percentiles for serum creatinine level were obtained and this defined the cutoff for renal impairment (labeled MONICA RI). Using this system, the cut off for abnormal renal function in men was creatinine >109.6 μmol/l and > 97.0μmol/l in women.

5.2.4 Deaths

All deaths up to an including 31st December 2006 were collated from the Scottish Registry office. From the information on death certificates, two experienced cardiologists (Professor Henry Dargie, Dr Theresa McDonagh) coded the deaths as cardiovascular, cancer, respiratory or other. The cardiovascular deaths were further sub classified as being due to MI, HF,

cerebrovascular disease or other. Where information on death certificates was missing or incomplete, the death was labelled as "uncoded".

5.2.5 Statistical analysis

The majority of continuous values were normally distributed and means were compared using an unpaired t-test or ANOVA as appropriate. Non-continuous variables were compared using a Mann-Whitney test or logarithmically transformed as necessary. Categorical variables were compared using χ^2 test. Correlation between continuous variables was assessed using Pearson's technique. ROC analysis was used to assess the ability of serum creatinine to correctly identify individuals with stage 3 CKD or worse.

Kaplan-Meyer analysis was used to compare survival and cardiovascular deaths between groups, with subsequent log-rank testing. Survival between groups was then assessed using Cox regression, and hazard ratios (HR) were calculated. Univariate analysis was performed initially, followed by multivariate analysis. As data on LV function, MI, IHD and hypertension was not contemporary with the eGFR data, two different multivariable models were designed for analysis of renal function and outcome; to be included, variables had to be significantly associated with mortality from the univariate analyses ($p < 0.10$). The first model included only contemporary data, that is, age and gender for all cause mortality and age alone for cardiovascular deaths. The second model included model 1, plus significant univariate variables from 1992 data; this incorporated LVEF, IHD, DM and hypertension.

All analysis was performed using SPSS or Minitab. A p value of less than 0.05 was considered statistically significant.

5.3 Results

5.3.1 Baseline characteristics

Eight hundred and fifty one individuals who attended for a rescreening visit in 1996 had samples available for creatinine estimation; thus these individuals were included in the final analysis. The characteristics of these patients are detailed in Table 5.1. The gender mix was almost equal, with slightly more females than males. Mean age at the rescreening visit was 53.7 ± 13.1 years; distribution of age is shown in Figure 5.1.

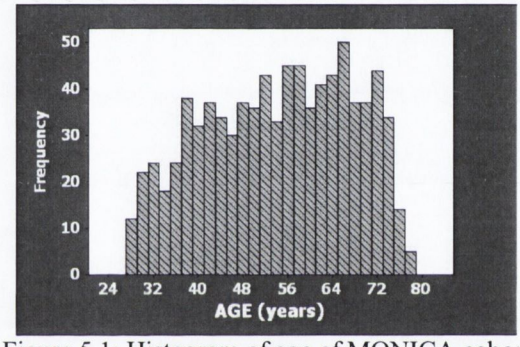

Figure 5.1: Histogram of age of MONICA cohort

The other variables in table 5.1 are from the original screening in 1992. As might be expected, this was a relatively well cohort with low rates of hypertension (22.2%), ischaemic heart disease (21.5%) and LVSD (6.0%). Symptoms were not widely reported with less than 10% reporting angina or breathlessness.

Males were younger than females, but not significantly so (53.2 ± 13.5 v 54.2 ± 12.8 years, p = 0.29). Males had higher rates of previous MI (6.0 v 3.2%, p = 0.05), diabetes mellitus (3.1 v 1.0%, p = 0.02) and LVSD (8.6 v 3.4%, p = 0.002) with a much lower mean LVEF (45.6 v 48.4%, p < 0.001); despite this, men were not significantly more likely to report angina than women (10.5 v 8.3%, p =0.26) and were actually half as likely to report breathlessness (6.7 v

12.4%, p = 0.003). This breathlessness could not explained by increased body weight as mean BMI did not differ between the genders (26.2 v 26.6, p =0.20). Rates of hypertension and ischaemic heart disease did not differ between men and women.

	Baseline characteristics	
		range
n	851	-
Age (years)	53.7	28 - 77
male	417 (49.0%)	-
BMI	26.4	15.7 – 52.3
Height (cm)	164.8	136.0 – 195.0
Weight (kg)	71.7	39.6 – 142.5
Systolic BP (mmHG)	132.5	84.0 – 222.0
Diastolic BP (mmHG)	78.5	41.0 – 119.0
Hypertension	189 (22.2%)	-
Diabetes Mellitus	17 (2.0%)	-
Previous M I	39 (4.6%)	-
Angina	80 (9.4%)	-
SOB	82 (9.6%)	-
IHD	183 (21.5%)	-
LVSD	51 (6.0%)	-
LVEF (%)	46.9	12.0 – 70.0
LVDD (cm)	4.9	3.1 – 6.9
LV diastolic volume	104.2	38.1- 258.7
LV systolic volume	55.9	12.8 – 203.8
LV mass	94.6	42.1 – 166.8
Exercise time	695.8	67 - 1094
HDL	1.47	0.61 – 3.67
NT-ANP*	1.3	0.1 – 13.6
BNP*	7.9	1.0 – 214.0

Table 5.1: Baseline characteristics of MONICA rescreen cohort

5.3.2 Renal Function

5.3.2.1 Serum Creatinine

Serum creatinine ranged from 51.3 to 304.3 μmol/l, with a median value of 83.1μmol/l; this is demonstrated in Figure 5.2A. Median (IQR) creatinine was significantly higher in men than women (89.1 (16.8) v 77.0 (15.0) μmol/l, p < 0.001). Higher creatinine concentration were

seen with older age, with those >60 years old having a significantly higher median (IQR) creatinine than those below this age (87.3 (20.4) v 80.9 (17.0) μmol/l, $p < 0.001$)

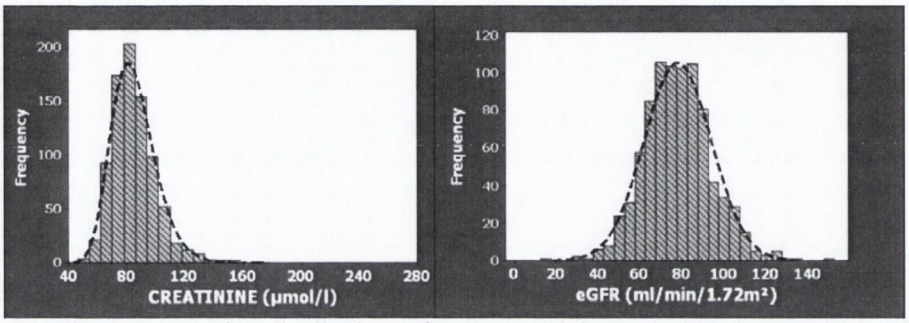

Fig 5.2: Histograms sowing distributions of serum creatinine and eGFR in MONICA cohort

Using NHANES criteria (93) for renal impairment based on serum creatinine concentration, 3.9% had abnormal renal function (3.4% of men, 4.3% of women). When Framingham criterion for renal impairment was used (67), only 1.9% of the study participants had abnormal renal function (1.4% of men, 2.3% of women).

Monica RI

From this cohort, a healthy reference sample was selected; this constituted individuals who were free of hypertension, DM, LVSD, angina and previous MI at the original 1992 screening (244). This incorporated five hundred and sixteen patients, 46% of which were male and a mean (SD) age of 49.7 ± 12.5 years. From these, a normal sex-specific 95th percentile for serum creatinine level was obtained and this defined the cutoff for renal impairment (labeled MONICA RI). Using this system, the cut off for abnormal renal function in men was creatinine >109.6 μmol/l and > 97.0μmol/l in women. When these cut-offs were applied to the entire cohort, seventy two (8.5%) had abnormal renal function based on serum creatinine. The characteristics of these individuals are detailed in Table 5.2.

	Normal Renal Function	MONICA RI	p value
n	779	72	
Age (years)	52.9 ± 13.0	62.4 ± 11.5	< 0.001
male	51.1	50.0	0.98
BMI	26.3 ± 4.5	27.4 ± 3.8	0.024
Systolic BP (mmHG)	131.9 ± 21.3	139.1 ± 22.7	0.012
Diastolic BP (mmHG)	78.4 ± 11.4	11.3 ± 11.3	0.55
Hypertension	20.6	42.3	< 0.001
Diabetes Mellitus	2.0	2.9	0.61
Previous M I	4.4	7.1	0.30
Angina	9.1	15.3	0.09
SOB	9.8	11.3	0.67
IHD	21.0	36.6	0.003
LVSD	6.4	9.4	0.36
LVEF (%)	47.2 ± 7.4	44.4 ± 9.4	0.023
HDL	1.48 ± 0.4	1.38 ± 9.4	0.03
NT-ANP*	1.26 (1.0)	1.82 (1.5)	< 0.001
BNP*	7.7 (8.8)	9.7 (12.1)	0.005

Table 5.2: Baseline characteristics of individuals with normal renal function v those with renal impairment (RI), defined by MONICA criteria

Those with MONICA RI were significantly older, although the gender mix was equal. Mean LVEF was lower in the MONICA RI group but rates of LVSD did not differ between the groups. Hypertension and IHD was more prevalent in those with MONICA RI.

5.3.2.2 eGFR

eGFR was normally distributed, as shown in figure 5.2B. Mean eGFR was 80.0 ± 16.1 ml/min/1.73m^2 and ranged from 13.9 to 147.6 ml/min/1.73m^2. The number (percentage) of individuals with (i) stage 1 or better CKD, (ii) stage 2 CKD, (iii) stage 3 CKD, (iv) stage 4 and (v) stage 5 or worse CKD was one hundred and seventy one (20.1%), five hundred and seventy nine(68.0%), one hundred (11.7%), one (0.1%) and zero (0.0%) respectively. Thus, very few individuals had advanced chronic kidney disease.

Lower GFR were seen with older age; there was a negative correlation between age (years) and eGFR ($r = -0.489$, $p < 0.001$). As CKD stage decreased, the proportion of patients in older age groups increased. Over three quarters of those with CKD stage 3 or worse were aged over 60 years old, compared to 11.6% of patients with stage 1 CKD or better being in this age group; this is demonstrated in Figure 5.3.

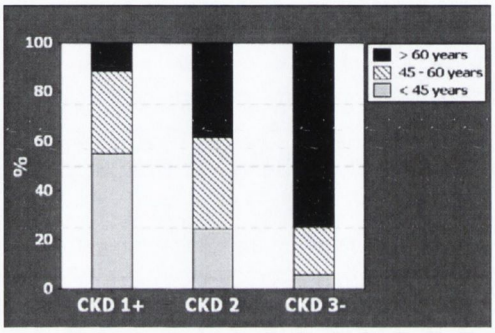

Figure 5.3: Barchart of age distribution of patients per CKD stage
[CKD 1 +, stage 1 CKD or better; CKD 3-, stage 3 CKD or worse]

eGFR was significantly lower in women than men (72.8 ± 14.6 v 83.3 ± 15.7 ml/min/1.73m^2, $p < 0.001$). As a result, the proportion of women increased as CKD status declined; for example, 23.4% of individuals with CKD stage 1 or better were female, compared to 74.3% of people with CKD stage 3 or worse. This is demonstrated figuratively in figure 5.4.

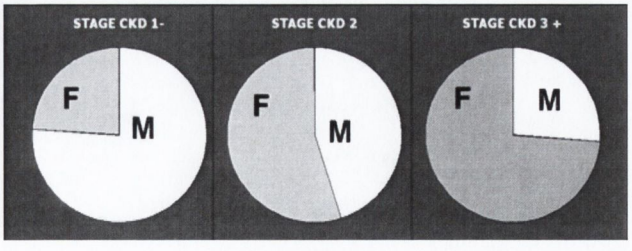

Figure 5.4: Distribution of gender per CKD stage.
[F, female; M, male; stage 1 CKD +, stage 1 CKD or better; stage 3 CKD -, stage 3 CKD or worse]

Table 5.3 shows the baseline characteristics of the cohort as a function of CKD status. Worse renal function was associated with increasing age, female gender, systolic blood pressure and higher rates of hypertension and IHD. As with Monica RI, lower CKD status was associated with a lower LVEF but not with a higher overall rate of LVSD.

	eGFR > 90	eGFR 60 - 90	CKD 3 -	p value
N	171	579	101	
Age (years)	44.4 ± 11.6	54.6 ± 12.4	64.4 ± 10.1	< 0.001
Male	76.0%	45.1	25.7	< 0.001
BMI	26.2 ± 5.0	26.3 ± 4.4	27.1 ± 3.8	0.23
Systolic BP (mmHG)	130.2 ±17.8	131.7 ± 21.8	141.5 ± 23.3	< 0.001
Diastolic BP(mmHG)	79.6 ± 11.4	78.1 ± 11.3	78.5 ± 11.6	0.31
Hypertension	15.4%	20.6%	44.6%	<0.001
Diabetes Mellitus	1.8%	2.3%	1.0%	0.66
Previous M I	2.3%	4.8%	6.9%	0.19
Angina	6.5%	9.8%	14.0%	0.13
SOB	8.9%	10.0%	11.1%	0.83
IHD	12.7%	23.6%	31.6%	0.001
LVSD	6.5%	6.7%	6.6%	0.99
LVEF (%)	45.7 ± 6.6	47.4 ± 7.6	45.9 ± 9.2	0.02
HDL	1.45 ± 0.3	1.48 ± 0.4	1.49 ± 0.4	0.73
NT-ANP*	0.96 (0.8)	1.34 (1.0)	1.99 (1.5)	<0.001
BNP*	6.1 (7.9)	8.0 (8.8)	12.1 (11.6)	0.001

Table 5.3: Baseline characteristics of MONICA cohort as a function of CKD status.

5.3.2.3 Ability of serum creatinine to identify renal impairment

Using a calculated eGFR of less than 60 ml/min/1.73m² as the definition of renal impairment, we can assess how accurate serum creatinine alone is in identifying renal impairment in the MONICA cohort. Figure 5.5 demonstrates that serum creatinine scored reasonably favourably.

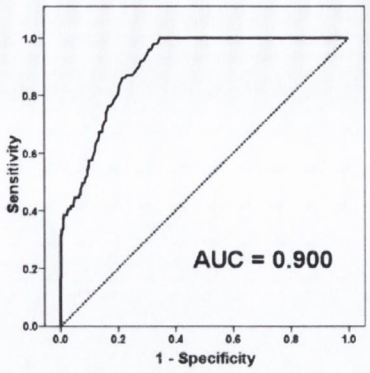

Figure 5.5: ROC curve demonstrating ability of serum creatinine to identify renal impairment in MONICA cohort

Using the MONICA criteria for identifying renal impairment proved to be very specific for identifying those with eGFR < 60 ml/min/1.73m², but had poor sensitivity; this is shown in Table 5.4. NHANES and Framingham criteria proved to be even more specific, but with very low sensitivity.

	sensitivity	specificity	PPV	NPV
MONICA	61.4%	98.7%	86%	95%
NHANES1	31.7%	99.9%	97%	91%
Framingham	15.8%	100%	100%	90%

Table 5.4: Ability of differing criteria of defining renal impairment using serum creatinine in identifying individuals in MONICA cohort with eGFR < 60 ml/min/1.73m²

Although using MONICA criteria had an acceptable negative predictive value, applying this to the cohort would have mistakenly defined thirty nine individuals as having normal renal function when they actually had eGFRs of less than 60 ml/min/1.73m²; this represents 38.2% of all individuals with an eGFR below this level. These false negatives were exclusively female and elderly, with a mean age of 65.4 ± 8.6 years. Conversely, MONICA criteria would have identified ten individuals as having renal impairment when they had eGFRs above 60 ml/min/1.73m², representing 14% of those with MONICA defined renal impairment. These false positives were exclusively male and were young, with a mean age of 53.6 ± 11.3 years.

5.3.3 Predictors of renal impairment

Table 5.5 details predictors of CKD grade 3 or worse, i.e. < 60ml/min/1.73m^2. Being aged over 60 years old was the strongest predictor of poor renal function, with an OR of 6.16 (3.86 – 9.82); using linear regression for age (years) and eGFR, it was calculated, eGFR = 110 – 0.6 age ($p < 0.001$); this is shown in figure 5.6.

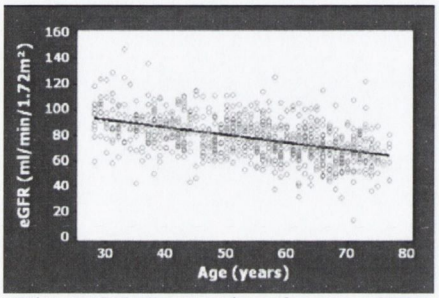

Figure 5.6: Scatterplot of age v eGFR

Female gender was also a strong predictor of poor renal function. Only hypertension and ischaemic heart disease proved to be predictive or renal function. LVSD had no significant correlation with renal impairment, and there was no significant relationship between LVEF or eGFR; eGFR = 83.6 – 0.12 LVEF, p = 0.12.

	OR (95% CI)	p value
Age > 60 years	6.16 (3.9 – 9.8)	< 0.001
Female	3.14 (2.0 – 5.0)	<0.002
IHD	1.73 (1.1 – 2.8)	0.02
Hypertension	3.34 (2.2 – 5.1)	<0.001
Diabetes mellitus	0.42 (0.1 – 3.5)	0.45
LVSD	0.99 (0.4 – 2.4)	0.98
Myocardial infarction	1.68 (0.8 – 3.9)	0.23
Angina	1.64 (0.9 – 3.0)	0.11
Breathlessness	1.15 (0.6 – 2.3)	0.65

Table 5.5: Logistic regression for predictors of renal impairment (eGFR < 60ml/min/1.73m^2)

A multivariate model was designed including all those variables with significant univariate associations with renal impairment. Following multivariate regression, ischaemic heart disease was no longer predictive (OR 0.9 (0.6 – 1.6), p = 0.79). However, age > 60 years (OR

5.6 (3.4 – 9.3), $p < 0.001$), hypertension (OR 2.4 (1.4 - 3.8), $p < 0.001$) and female gender (OR 3.6 (2.1 – 5.7), $p < 0.001$) all remained independent predictors of renal impairment.

5.3.4 Outcome

All deaths were recorded up to and including the 31st December 2006. Mean follow up was 10.1 ± 0.3 years. Of the eight hundred and fifty one individuals included in the study, one hundred and nine (12.8%) had died by this date. As demonstrated in figure 5.7, the rate of death was linear throughout the follow up period.

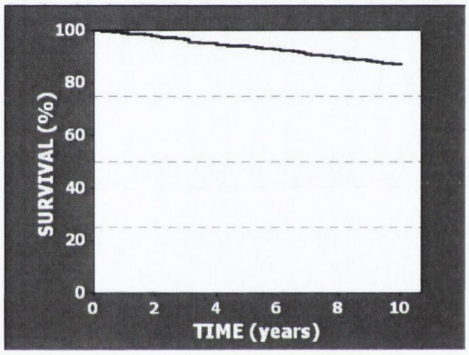

Figure 5.7: Kaplan-Meier curve of survival of MONICA cohort during 10 year follow up period

The deaths were coded thus:

- Cardiovascular deaths 45 (41.3% of all deaths)
- Cancer deaths 33 (30.3%)
- Respiratory deaths 12 (11.0%)
- Other 12 (11.0%)
- Uncoded 7 (6.4%)

Of the cardiovascular deaths, seventeen (37.8%) were attributed to a myocardial infarction, ten (22.2%) to heart failure and ten (22.2%) to a cerebrovascular accident. Eight (17.8%) had

another cardiovascular death another cause of cardiovascular death listed, for example, ruptured aortic aneurysm, mesenteric ischaemia or valvular heart disease.

Of the thirty three deaths attributed to cancer, lung cancer was the commonest primary source with seventeen (51.5%). Nine (27.3%) had a gastro-intestinal malignancy, three (9.1%) has cancer of the uro-genital tract and the remaining four (12.1%) had malignancy from another source.

Increasing age was unsurprisingly a strong predictor of all cause mortality, and also of cardiovascular death. Kaplan-Meier curves for those aged >60 years against those aged <60 years are shown in figure 5.8. The mortality rate was very low for those aged under 60 years old, with only a 6.0% all cause mortality rate and a 1.8% cardiovascular death rate; respective rates for those ages >60 years was 24.3% and 12.0%.

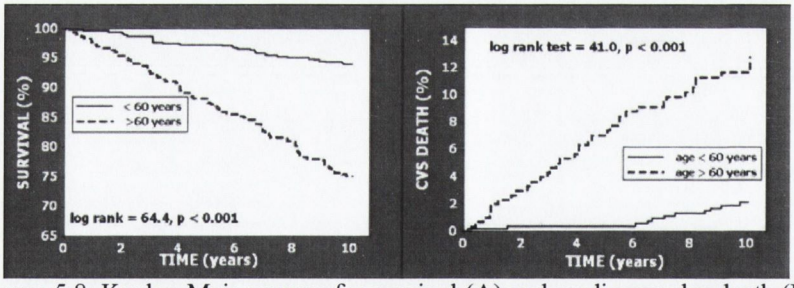

Figure 5.8: Kaplan-Meier curves for survival (A) and cardiovascular death (B) comparing those aged < 60 and >60 years

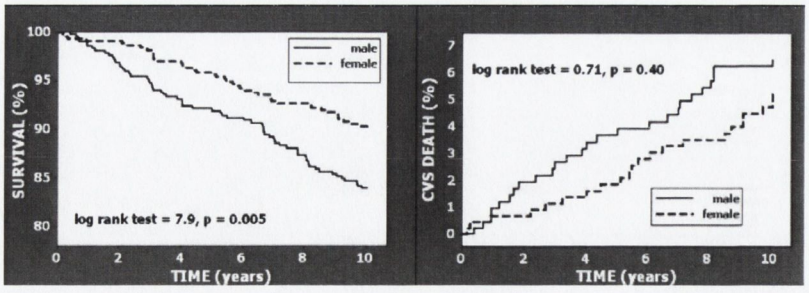

Figure 5.9: Kaplan-Meier curves for survival (A) and cardiovascular death (B) comparing men and women

Male gender was also associated with poorer outcome as demonstrated in Figure 5.9. Males had a significantly higher all cause mortality. Although the rate of cardiovascular death was also higher in men, this did not reach statistical significance.

5.3.4.1 Predictors of outcome

Univariate HRs for age (continuous variable) and gender are shown in table 5.6, for both all cause mortality and cardiovascular death. This table also demonstrates HRs for variables from the original 1992 screening; LVSD, angina and hypertension were all strong univariate predictors of poor outcome but DM and previous MI had the most impressive HR, particularly for cardiovascular death. There was a trend toward better outcome with increasing HDL cholesterol, but these were not statistically significant. The reporting of breathlessness by patients was not associated with increased all cause mortality, nor of cardiovascular death.

A multivariate model for all cause mortality was designed including age, gender, LVSD, ischaemic heart disease, diabetes mellitus, HDL, breathlessness and hypertension. A similar model was designed for cardiovascular deaths using the same variables, with the exception of breathlessness and gender. Adjusted HRs following multivariate analysis are detailed in Table 5.7. Age remained an independent predictor of both all cause mortality and of cardiovascular death. LVSD, diabetes mellitus and hypertension were independent predictors of all cause mortality but not of cardiovascular death. Ischaemic heart disease was not predictive of all cause mortality but there was a trend toward an independent predictor of adverse cardiovascular death. Higher HDL was independently associated with a better cardiovascular outcome, and was almost independently predictive of all cause mortality.

	All cause mortality		Cardiovascular death	
	HR (95% CI)	p value	HR (95% CI)	p value
Age*	1.084 (1.06 – 1.11)	<0.001	1.102 (1.06 – 1.14)	<0.001
Male	1.73 (1.17 – 2.54)	0.005	1.28 (0.73 – 2.25)	0.40
LVEF*	0.958 (0.94– 0.98)	<0.001	0.94 (0.91 – 0.96)	<0.001
LVSD	3.35 (1.99 – 5.65)	<0.001	3.56 (1.66 – 7.67)	0.001
Myocardial infarction	3.91 (2.26 – 6.74)	<0.001	6.46 (3.21 – 13.0)	<0.001
Diabetes Mellitus	6.01 (3.04 – 11.9)	<0.001	6.08 (2.12 – 17.0)	<0.001
Angina	2.94 (1.85 – 4.67)	<0.001	4.88 (2.56 – 9.20)	<0.001
Ischaemic heart disease	2.76 (1.88 – 4.05)	<0.001	4.69 (2.64 – 8.34)	<0.001
Hypertension	2.64 (1.80 – 3.88)	<0.001	3.78 (2.14 – 6.65)	<0.001
HDL*	0.64 (0.38 – 1.08)	0.09	0.45 (0.19 – 1.04)	0.06
Breathlessness	1.56 (0.92 – 2.75)	0.10	1.18 (0.47 – 3.01)	0.71

Table 5.6: Univariate hazard ratios for all cause mortality and cardiovascular deaths in the MONICA cohort (*continuous variables)

	All cause mortality		Cardiovascular death	
	HR (95% CI)	p value	HR (95% CI)	p value
Age*	1.065 (1.04 – 1.09)	< 0.001	1.10 (1.05 – 1.14)	< 0.001
Male	1.28 (0.81 - 2.02)	0.30	--	--
LVSD	2.03 (1.12 – 3.38)	0.02	1.98 (0.82 – 4.76)	0.12
Diabetes Mellitus	2.76 (1.23 – 6.20)	0.01	1.76 (0.49 – 6.30)	0.39
Ischaemic heart disease	1.26 (0.78 – 2.00)	0.34	1.85 (0.95 – 3.58)	0.07
Hypertension	1.93 (1.23 – 3.04)	0.04	1.81 (0.95 – 3.45)	0.07
HDL*	0.55 (0.30 – 1.02)	0.057	0.39 (0.15 – 0.98)	0.045
Breathlessness	1.33 (0.74 – 2.41)	0.34	--	--

Table 5.7: Multivariate hazard ratios or all cause mortality and cardiovascular death in the MONICA cohort (*continuous variables)

5.3.5 Renal Function and Outcome

5.3.5.1 Creatinine

Kaplan-Meier curves for all cause mortality and cardiovascular death are shown on figure 5.10, based on the cohort being defined as having renal impairment based on MONICA, NHANES and Framingham criteria. As demonstrated, renal impairment was associated with poorer long term outcome, regardless of the method used to define it.

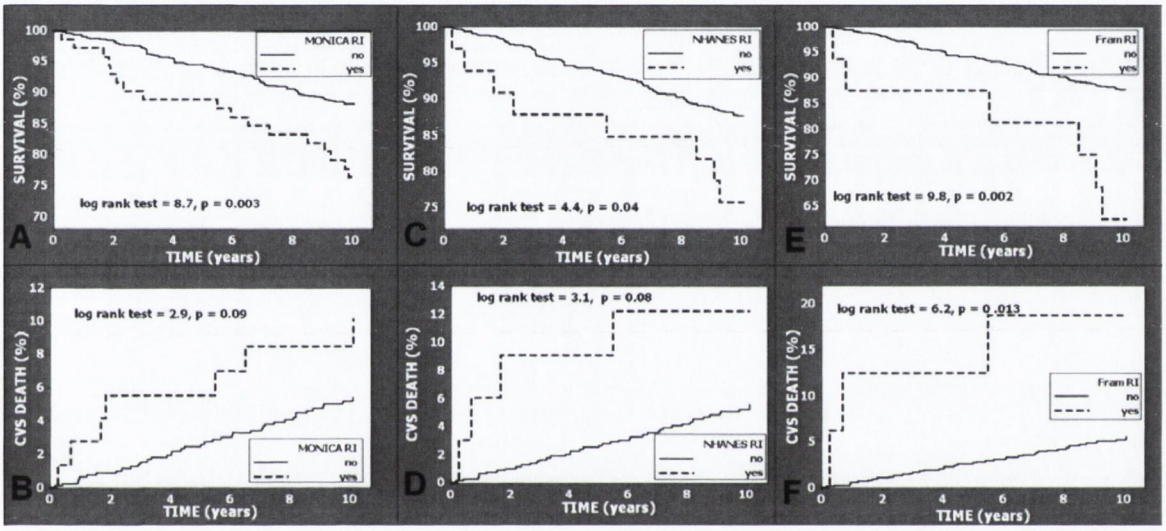

Figure 5.10 Kaplan-Meier curves for differing definitions of renal impairment based on serum creatinine. Include survival (A) and cardiovascular death (B) for MONICA RI, survival (C) and cardiovascular death (D) for NHANES RI and survival (E) and cardiovascular death (F) for Framingham RI.

Univariate HRs for all cause mortality are detailed in table 5.8. Increasing creatinine (continuous variable) was associated with poorer long term outcome, and remained an independent predictor of adverse outcome, when adjusted for age and gender, and even when adjusted for these variables plus LVEF, ischaemic heart disease, hypertension and diabetes mellitus. The Framingham criteria for renal impairment provided the strongest univariate HR for poor outcome, and remained an independent predictor of outcome even when adjusted for age and gender, and also when other variables were included.

	Univariate HR HR (95% CI)	p value	Adjusted for model 1[a] HR (95% CI)	p value	Adjusted for model 2† HR (95% CI)	p value
Creatinine	1.026 (1.02 -1.03)	< 0.001	1.014 (1.00 – 1.03)	0.012	1.016 (1.01 – 1.03)	0.006
Monica RI	2.14 (1.28 – 3.60)	0.004	1.20 (0.71 – 2.04)	0.49	1.18 (0.66 – 2.10)	0.58
NHANES RI	2.12 (1.03 – 4.36)	0.04	1.27 (0.62 – 2.63)	0.51	1.69 (0.80 – 3.58)	0.17
Framingham RI	3.43 (1.50 – 7.81)	0.003	2.27 (0.99 – 5.21)	0.05	3.32 (1.41 – 7.84)	0.006

Table 5.8: Unadjusted and adjusted hazard ratios for all cause mortality in MONICA cohort; creatinine [[a]age and gender †as per model 1, plus LVEF, IHD, DM and hypertension]

HRs for cardiovascular death are detailed in table 5.9. Increasing creatinine, assessed as a continuous variable, was independently associated with poorer cardiovascular outcome, even when adjusted for age, LV function, ischaemic heart disease, diabetes mellitus and hypertension. Neither the NHANES nor MONICA definitions of renal impairment were univariate or multivariate predictors of outcome. Framingham renal impairment was a strong univariate predictor of adverse cardiovascular outcome, with a four-fold increased risk compared to those without renal impairment. When adjusted for age alone, Framingham renal impairment was no longer predictive, but when model 2 was applied, became independently predictive of poor outcome with an adjusted HR of 3.50 (1.03 – 11.8).

	Univariate HR HR (95% CI)	p value	Adjusted for model 1[a] HR (95% CI)	p value	Adjusted for model 2† HR (95% CI)	p value
Creatinine	1.027 (1.02 – 1.04)	< 0.001	1.019 (1.01 – 1.31)	0.002	1.02 (1.01 – 1.03)	0.008
Monica RI	1.98 (0.88 – 4.40)	0.10	1.03 (0.46 – 2.32)	0.94	0.84 (0.34 – 2.07)	0.70
NHANES RI	2.43 (0.88 – 6.77)	0.09	1.34 (0.48 – 3.76)	0.57	1.91 (0.66 – 5.51)	0.24
Framingham RI	3.94 (1.22 – 12.6)	0.02	2.20 (0.68 – 7.12)	0.19	3.50 (1.03 – 11.8)	0.04

Table 5.9: Unadjusted and adjusted hazard ratios for cardiovascular death in MONICA cohort: creatinine [[a]age †as per model 1, plus LVEF, IHD, DM and hypertension]

5.3.5.2 eGFR

Lower eGFR was associated with poorer outcome in terms of both all cause mortality and cardiovascular death. Overall, those with an eGFR < 60 ml/min/1.73m² had a higher all cause mortality and cardiovascular death rate compared to those with eGFR >60 ml/min/1.73m²; this is demonstrated in Kaplan-Meier curves in figure 5.11. There was a stepwise increase in adverse outcome over the follow up period in those at CKD stage 1 or better, CKD stage 2 and CKD stage 3 or worse, again demonstrated figuratively in Fig 5.11.

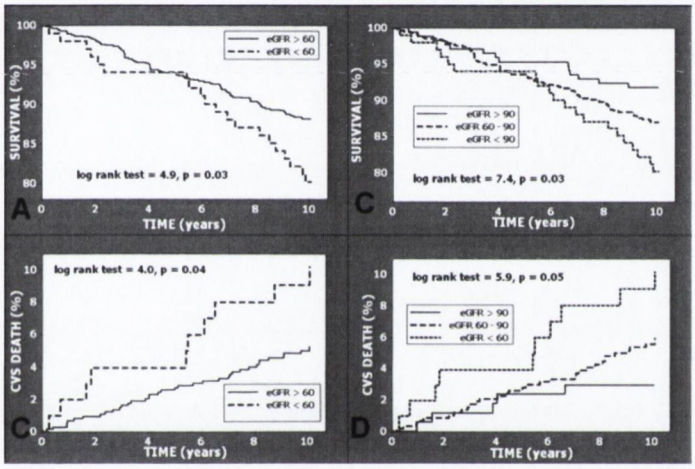

Figure 5.11: Kaplan-Meier curves for MONICA cohort. (A) all cause mortality eGFR > v eGFR > 60 ml/min/1.73m², (B) cardiovascular death eGFR > v eGFR > 60 ml/min/1.73m² (C) All cause mortality per CKD status, (D) cardiovascular death per CKD status.

Lower eGFR, assessed as a continuous variable, was a univariate predictor of all cause mortality but was not an independent predictor of outcome following adjustment for age, nor after multivariate analysis. Results are summarised in table 5.10. Having an eGFR < 60 ml/min/1.73m² carried an unadjusted HR of 1.71 (1.06 – 2.78) for all cause mortality, but was not predictive of outcome after multivariable analysis. A similar outcome was seen with CKD staging, using CKD stage 1 or better as reference; CKD stage 3 or worse was a strong univariate predictor of adverse outcome (HR 2.52) but CKD staging proved not to be

independently predictive of outcome following adjustment for age, and subsequently for the other variables.

	Univariate HR HR (95% CI)	p value	Adjusted for model 1[a] HR (95% CI)	p value	Adjusted for model 2† HR (95% CI)	p value
eGFR	0.974 (0.96 – 0.99)	< 0.001	0.993 (0.98 – 1.00)	0.35	0.992 (0.98 – 1.00)	0.34
CKD (eGFR < 60)	1.71 (1.06 – 2.78)	0.03	0.95 (0.57 – 1.58)	0.83	0.84 (0.46 – 1.50)	0.55
eGFR > 90	1.0		1.0		1.0	
eGFR 60 – 90	1.61 (0.91 – 2.85)	0.10	0.81 (0.44 – 1.49)	0.50	0.80 (0.41 – 1.58)	0.54
eGFR < 60	2.52 (1.27- 5.00)	0.008	0.77 (0.35 – 1.68)	0.52	0.69 (0.29 – 1.620	0.39

Table 5.10: Unadjusted and adjusted Hazard ratio for all cause mortality in MONICA cohort; eGFR [[a]age and gender †as per model 1, plus LVEF, IHD, DM and hypertension]

	Univariate HR HR (95% CI)	p value	Adjusted for model 1[a] HR (95% CI)	p value	Adjusted for model 2† HR (95% CI)	p value
eGFR	0.967 (0.95 – 0.98)	< 0.001	0.997 (0.97 – 1.02)	0.79	0.996 (0.97 – 1.02)	0.70
CKD (eGFR < 60)	2.01 (1.00 – 4.03)	0.05	0.84 (0.41 – 1.73)	0.64	0.68 (0.30 – 2.07)	0.36
eGFR > 90	1.0	-	1.0	-	1.0	-
eGFR 60 – 90	1.99 (0.78 – 5.10)	0.25	0.72 (0.27 – 1.94)	0.52	0.82 (0.28 – 2.46)	0.78
eGFR < 60	3.53 (1.21 – 10.3)	0.02	0.62 (0.19 – 2.0)	0.42	0.57 (0.16 – 2.06)	0.39

Table 5.11: Unadjusted and adjusted Hazard ratio for cardiovascular death in MONICA cohort; eGFR [[a]age †as per model 1 plus LVEF, IHD, DM and hypertension]

Similarly for cardiovascular deaths, eGFR was a univariate but not multivariate predictor of adverse outcome- results are summarised in table 5.11. Having an eGFR < 60ml/min/1.73m^2 had a univariate HR of 2.01 for cardiovascular death, but wasn't independently predictive of outcome after multivariate analysis. Having stage 3 CKD or worse had a univariate HR for

cardiovascular death of 3.53, but as with all cause mortality, CKD staging proved not to be predictive of outcome after adjustment for model 1 or model 2.

5.2.5.3 Gender, eGFR and outcome

Figure5.12 demonstrates crude all cause mortality and cardiovascular death rates for men and women per 10 point fall in eGFR. We can see that for all cause mortality, the crude rate in men appears to increase once eGFR falls below 80ml/min/1.73m², but only increases significantly in women once eGFR falls below 70 ml/min/1.73m².

Similarly for cardiovascular death rates, the crude rate increases in men again once eGFR falls below 80 ml/min/1.73m² but the rate in women only jumps upward once eGFR falls below 70ml/min/1.73m².

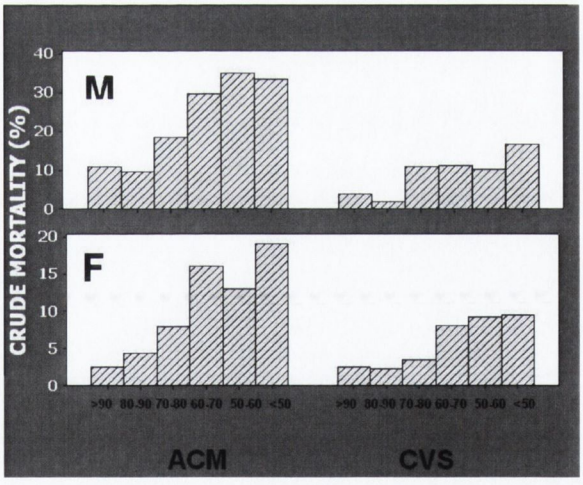

Figure 5.12: Crude mortality rate for all cause mortality and cardiovascular death for males (M) and females (F) per 10 point change in eGFR.

The interaction and influence of gender and eGFR on long term outcome is demonstrated in table 5.12. Using female gender with an eGFR > 90ml/min/1.73m² as reference, we can see that unadjusted HR for all cause mortality is higher in males and increases dramatically as

eGFR falls. Compared to a female with eGFR > 90ml/min/1.73m², a male with CKD stage 3 or worse has over 16 times the risk of death.

eGFR (ml/min/1,72m²)	Females	Males
> 90	1.0	4.7
80-90	1.9	4.1
70-80	3.3	8.3
60-70	7.3	14.5
50-60	5.6	17.6
< 50	8.5	16.7

Table 5.12: Unadjusted hazard ratios for all cause mortality per gender and 10 point incremental fall in eGFR

5.4 Discussion

Not unexpectedly, this cohort of the general population of Glasgow proved to reasonably healthy, with low levels of co-morbidities comparable to those quoted in other similar studies. Only 2% had DM, almost half the rate seen in Garg et al's (93) cohort and significantly lower than the 6% and 10% quoted by Culleton et al (67) and Go et al (71) respectively. The 22.2% prevalence of hypertension is very similar to that seen in these latter two studies also, but approximately half that seen in Garg et al. The 4.6% prevalence of previous MI in the Glasgow cohort is only slightly lower than the prevalence of coronary heart disease of 6% and 10% found by Culleton et al and Go et al. The overall rate of IHD in this cohort seems quite high at 21.5% but this probably reflects the broad definition used for this.

Given that the major epidemiological studies of the general population assessing renal function and outcome are broadly similar, it is thus a little surprising to see them exhibit a wide range in renal function. Some studies quoted a prevalence of only 3% of their cohorts having an eGFR of less than 60ml/min/1.73m²(72,118); in other cohorts of similar age, the rate of eGFR< 60m l/min/1.73m² was as high as 10 to 18% (68,71,75). The prevalence of CKD stage 3 or worse in this cohort is therefore not extreme at 11.5%.

Certainly renal function in this cohort was much better than that seen in the earlier studies. Only 1.9% of this cohort fulfilled Framingham criteria for a diagnosis of mild renal impairment based on serum creatinine, compared to 8.7% of men and 8% of women when this criterion was applied to the Framingham cohort itself (67). Similarly, only 3.9% of this study group fulfilled a diagnosis of renal impairment using NHANES criteria, compared to 9.4% of the NHANES cohort (93). This is difficult to explain, given that the Glasgow cohort was of a similar age to, Framingham and NHANES; as discussed though, these earlier cohorts had a much higher prevalence of hypertension and/or DM.

IHD was a strong univariate predictor of renal impairment in this group, but did not remain an independent predictor of CKD stage 3 after multivariate analysis. Hypertension proved to have a strong association with reduced renal function in this cohort, not unexpected given that hypertension is the second commonest cause of ESRF in the general population (27). The commonest cause of ESRF is DM, although no association (even univariate) was seen between this and renal impairment; this is probably explained by the very low prevalence of DM in the cohort. Age and female gender were both strong independent predictors of CKD stage 3 or worse. Increasing age has a well documented association with decreasing renal function (27,33,53) and given that females have a lower mean eGFR than males, it would be expected that they are more likely to have an eGFR less than 60ml/min/1.73m^2.

These findings highlight the limitations in using serum creatinine alone as a method of identifying individuals with renal impairment. Using MONICA criteria or renal impairment based on serum creatinine > 109.6μmol in men and > 97.0μmol/l in women, 38.2% of all individuals with an eGFR of less than 60ml/min/1.73m^2 would have been misclassified as

having normal renal function; these individuals were elderly and exclusively female. Thus, individuals who are most likely to have significant renal disease are, by using serum creatinine alone, most likely to be missed!

Overall, 12.8% of the cohort died during the follow up period, giving an approximate annual mortality rate of 1.2% per year. No previous studies have a mortality rate lower than this, although Garg at al (93) and Meisenger et al (68) had as similar rate. Others had a mortality rate approximately 30% (71) to 80% (67) higher than this. The annual cardiovascular death rate in the MONICA cohort was 0.5%, which was very similar to that quoted elsewhere (68,93). Increasing age and poor LV function were strong independent predictors of both all cause mortality and cardiovascular death, whilst both DM and hypertension were multivariate predictors of all cause mortality.

Women had a lower overall mortality rate than men in addition to having a lower eGFR. Thus for any particular eGFR, the crude mortality in men was significantly higher. Figure 5.12 demonstrates that for an eGFR between 60 and 70 ml/min/1.73m^2, the crude mortality rate was twice that in men than in women (30% v 15%); this figure also demonstrates that cardiovascular crude mortality only steps up in women when eGFR falls below 70ml/min/1.73m^2, when the first step up in men is seen once eGFR falls below 80ml/min/1.73m^2. As shown in table 5.12, (when compared to a women with eGFR > 90ml/min/1.73m^2) a man with eGFR between 70 and 80 ml/min/1.73m^2 has the same unadjusted hazard ratio for all cause mortality as a women with an eGFR of less than 50ml/min/1.73m^2. All of this adds weight to the argument for reclassification of CKD staging taking gender into account (36).

eGFR and CKD status were univariate, but not multivariate, predictors of both all cause mortality and cardiovascular death. Perhaps a surprising result at first glance, further analysis reveals this finding not to be completely incongruous with previous comparable studies. Certainly, two large studies failed to identify mild to moderate renal disease as being independently predictive of all cause mortality (68,93) and the majority of other studies only concluded that renal impairment was associated with adverse cardiovascular outcome only. Furthermore, the low risk profile of this MONICA cohort and a low rate of end-points (i.e. death) make it more difficult to identify any independent predictors of outcome, particularly with a relatively small sample size. This is supported by the observation that the mortality rate in this cohort is as similarly low as the two quoted studies that showed no association with renal impairment and mortality (68,93).

Of course, the Framingham criterion for renal impairment was a multivariate predictor of poor outcome in this group, although neither the MONICA or NHANES criteria were. Thus, one can conclude that there was evidence in this cohort that mild to moderate renal impairment was an independent predictor of all cause mortality and cardiovascular death. It must be recognised though that the Framingham criteria for renal impairment was the most stringent, and thus included only those with the very worst renal function.

5.4.1 Limitations

This study had a number of limitations that should be acknowledged. Information on urinanalysis (e.g. proteinuria or haematuria) might have been helpful in distinguishing and risk stratifying renal impairment. Classification of death as cardiovascular based on information on a death certificate is not a robust method. Information on cardiovascular

morbidity (further MI, hospital admission with HF etc) would have been desirable. Smoking is recognised as a major factor influencing adverse cardiovascular outcome. This study was limited in reliable smoking data was not available. The non-contemporary nature of the serum creatinine and the data on LV function and medical history is a major limitation. Stored serum samples from the 1992 screening were not available, as were reliable data from echo and personal questionnaires from 1995.

5.4.2 Conclusion

In this Glasgow cohort of the general population, renal impairment was not common with only 11.5% having CKD stage 3 or worse. This was more likely in older individuals, females and those with hypertension. The overall risk profile of the cohort was not high, reflected by a crude mortality rate of only 12.8% in the 10 years of follow up.

eGFR and CKD status were univariate but not multivariate predictors of either all cause mortality or cardiovascular death. This finding is in keeping with some similar studies of low risk groups but may also be explained by low event rates and relatively small sample size. Mild to moderate renal impairment, using Framingham criteria of cut-offs in serum creatinine, was independently predictive of all cause mortality and cardiovascular death; however, this cut-off was relatively high and only included the 1.9% of the cohort with the very worst renal function.

CHAPTER 6

GENERAL DISCUSSION AND CONCLUSIONS

Although improvements continue to be seen (9,10), Scotland continues to have the highest rate of cardiovascular morbidity and mortality (1) in the United Kingdom; a number of different factors contribute to this including genetics, lifestyle choices and socioeconomic status. Any simple method of identifying high risk individuals within the community should be studied and exploited in order to better direct therapies and healthcare expenditure, with the ultimate aim of improving the health of the nation. A simple measure of renal function could perform this task, as it is now increasingly recognised that even mild forms of renal impairment independently predicts adverse outcome in both the general population and in those with established cardiovascular disease. The primary aim of this thesis was to investigate the range of renal function and prevalence of renal disease within different cohorts of the Glasgow population, and to ascertain whether mild to moderate renal function was independently associated with outcome. An additional aim was to investigate change in renal function over time in a Glaswegian post-MI cohort and correlate this with outcome.

6.1 Renal function and outcome

The relative novelty of investigating renal function and outcome is highlighted by the finding that serum creatinine was not routinely measured at the initial screening visits for any cohort in 1995, or even in the post-MI rescreen visit in 1998. Serum glucose, lipid levels and natriuretic peptide levels were measured at these visits, reflecting current thinking regarding cardiovascular risk at that time and the absence of any assessment of renal function is noteworthy.

Chapters 2, 4 and 5 have concentrated on assessing renal function and outcome in a post MI cohort, a cohort from primary care on HF therapy and a cohort of the general population

respectively. Common themes seen in all three cohorts included: higher prevalence of renal disease in elderly patients; misclassification of elderly women as having normal renal function when serum creatinine cut-offs used; lower eGFR in women and; increased representation of women in lower CKD stages. These findings agree with the majority of published evidence and form the main arguments for reclassification of CKD stage based on gender and age (36). In keeping with other published data (119), no cohort demonstrated a univariate association between renal function and LV size or systolic function.

Unsurprisingly, largely as a function of age, renal function was a strong univariate predictor of all cause mortality and cardiovascular death. However, in all three cohorts, it was found that mild to moderate renal impairment was independently predictive of outcome, although differing classifications of renal impairment were required in each cohort. Interestingly, CKD stage 3 or worse was not a multivariate predictor of outcome in any group. eGFR proved to be independently predictive of cardiovascular death only in the GP-HF cohort, and only after dividing the cohort into quartiles based on eGFR; of note, the same system failed to yield similar results in the POST MI cohort. Although an outdated method of defining renal function, cut-offs for serum creatinine proved to be multivariate predictors of outcome in all three cohorts.

The poor performance of eGFR and CKD status at predicting outcome was thus a little surprising, particularly when compared to other studies assessing eGFR and outcome (38,39,42,46-48,68,72,80,89,90,118,127,133,243). This deserves further assessment. As detailed in the discussion sections of the individual chapters, the relatively low risk profile and low end point rate of both the POST MI and MONICA cohorts could explain this.

Certainly, when compared to published post- MI and HF studies, the studies assessing mild to moderate renal impairment in the general population were less definite in their conclusions regarding its influence on outcome with some even finding no independent association with all cause mortality (67,68,93). If we are to then compare the low risk Glasgow MONICA cohort with these studies, it is therefore not extraordinary to find no independent association between CKD status, eGFR and outcome. Similarly with the POST MI cohort, given that the individuals were screened many years after their MI, and thus a self selected group of "survivors", it is difficult to directly compare the findings in this thesis with other publications.

Of course, in both the POST MI cohort and MONICA cohort, cut-offs in serum creatinine did prove to be independently predictive of adverse outcome. This may be due to this method preferentially selecting men. Furthermore, in the MONICA cohort, it was only the Framingham criteria of renal impairment that proved to independently predict adverse outcome; this was actually as the highest cut-off values and therefore selected only those with the very worst renal function. Different cut-offs of serum creatinine were used in each cohort, using methods used elsewhere previously; as such, one single method of defining renal impairment using serum creatinine can not be used in all individuals.

In both the post-MI and GP-HF cohorts, an association was found between renal impairment and death attributable to HF. This finding makes sense; impaired excretion of water and sodium due to reduced glomerular filtration would exacerbate problems with fluid homeostasis, natriutretic peptide secretion and RAAS activation. However, this finding is

only observational, and limited by the relatively small number of deaths due to HF, and that HF was diagnosed from death certificate analysis.

When analysing the cohorts, all individuals with an eGFR below a certain level, or serum creatinine above a certain level were all grouped together and compared with individuals with better renal function. Given that severe renal disease is unquestionably associated with adverse cardiovascular disease and that this thesis was interested in the influence of milder forms of renal impairment, it may be a justifiable concern that individuals with severe renal disease might "contaminate" the renal impairment groups, leading to a misleadingly high rate of death and cardiovascular death within the renal impairment group as a whole. This concern should be addressed when it is clarified that no individuals in any cohort was receiving renal replacement therapy; furthermore if we look at the range of renal function in the cohorts, we can see that very few individuals indeed had even CKD stage 4 or worse. Very few, if any, individuals would have been attending a renal clinic. Thus, it can be concluded that in the MONICA, POST-MI and GP-HF cohorts, mild to moderate renal impairment was independently associated with adverse outcome.

6.2Change in renal function

Perhaps the most novel aspect of this thesis, and thus its most interesting facet, is tracking the change in renal function over time following MI and correlating this with long term prognosis. This is detailed in Chapter 3. It certainly appears that assessing change in renal function over time is emerging as a new frontier in investigating cardiorenal interaction; this statement is based on the observation that the majority of studies pertaining to this have been published within the past half-decade (95,104,106,108-111,115-117).

In contrast to chapters 2, 4 and 5, it seems that eGFR performed better than serum creatinine, especially with regard to predicting outcome. Saying this, the adjusted hazard ratios for all cause mortality and cardiovascular death for those who had a rise in serum creatinine of > 26.5μmol/l (i.e. WRF) were impressive. However, this applied to only a very small proportion of individuals, reflecting the more stable nature of renal function relatively well non-hospitalised patients. It would appear that future studies monitoring chronic change in renal function may be better served by utilising eGFR, or using smaller increases in serum creatinine as defining WRF.

6.3 BNP

A number of recognised findings regarding natriuretic peptides, and BNP in particular, where found to be also true in these Glasgow cohorts. In all these cohorts, raised BNP was associated with increasing age, female gender, LV systolic dysfunction and heart failure; these associations have been described elsewhere previously. The strong prognostic strength of BNP was also evident in the post MI and GP-HF cohorts, also consistent with studies performed elsewhere (206,208-210,218,233).

Of particular interest to this thesis was the association between natriuretic peptides and renal function. In keeping with other evidence, a definite inverse relationship between renal function and BNP concentration was demonstrated in these Glasgow cohorts. As discussed in the introduction section, this is likely related to reduced renal excretion of BNP, increased LV wall stretch due to salt and water retention and higher prevalence of cardiovascular disease seen with reduced renal function. The diagnostic potential of BNP was not as robust as its prognostic strength; in the post-MI cohort, it performed modestly in identifying LVSD within

the group and performed comparably to renal function in identifying HF in the GP-HF cohort. Furthermore, tracking change in BNP over time provided to add no additional prognostic information in the post MI cohort; this adds to the growing consensus that sequential BNP estimation is less useful than a one-off assessment, particularly with chronic disease processes.

One finding of note in Chapter 3 was that raised BNP was associated with a more marked fall in eGFR following MI. Whether this finding is mirrored in other populations remains to be seen but if this proved to be the case, BNP could potentially act as useful marker in renal medicine, possibly in identifying those individuals at higher risk of progressing to ESRF. Despite its undoubted prognostic strength in cardiovascular disease, BNP has yet to really find a definite role at a practical level in cardiology, and perhaps widening its range to include other specialities may be more fruitful.

6.4 Interpretation of results

Thus, it has been demonstrated in this thesis that even milder forms of renal impairment are independently predictive of premature mortality in differing cohorts of the Glasgow population; this confirms findings seen in other populations. The possible explanation for this association has already been discussed in the Introduction section; briefly, it could be explained by an excess of traditional cardiovascular risk factors seen in those with reduced renal function and the presence of increasingly recognised non-traditional risk factors, and by activation of the RAAS.

It must be stated that results from chapters 2, 4 and 5 cannot by themselves provide any further insight into cardiorenal interaction in either the general population or in those with established cardiovascular disease. On the other hand, chapter 3 and its insights into change in renal function and prognosis, in addition to the other recent evidence, does perhaps shed further light. Inadequately controlled cardiovascular risk factors, particularly hypertension and DM, may explain both deteriorating renal function and poor prognosis. The observation that raised BNP predicted a larger subsequent fall in renal function possibly merits further scrutiny. Raised BNP reflects high LV wall stress, and thus acts as a marker of more advanced haemodynamic and hormonal deregulation; it thus acts a much better marker of cardiovascular disease state than, for example, LVEF. Extrapolating this, one could postulate that renal dysfunction and worsening renal function may therefore simply act surrogate markers of the severity of cardiovascular disease state and adverse hormonal activation, particularly the RAAS. Another possibility is that accelerated decline in renal function may represent on-going systemic inflammation, itself well recognised as predictive of poor cardiovascular outcome (111,135-137,139,140,142,143); furthermore, systemic inflammation itself may reflect an active widespread atherosclerotic process.

6.5 Strengths and Limitations

There are a number of strengths and limitations in the production of this thesis which must be discussed. Firstly, one must reflect that although the screening studies performed in the 1990s incorporated an average of almost 1000 individuals per cohort, these numbers are small when compared to other population based studies assessing renal disease and outcome, with some studies involving over one million patients. However, one advantage of the relatively small

size of the Glasgow cohorts is that the patient data collated is much more extensive and accurate, including LV function, symptomatology, medication and co-morbidities.

One must acknowledge that the original CRI screening visits were not specifically designed with a view to investigating renal impairment and cardiovascular disease. More information regarding renal function at time of screening visits would have been very desirable, specifically looking for (and quantifying) proteinuria. This would have been particularly helpful in further defining CKD stage 1 and 2. eGFR becomes less accurate above 60ml/min/1.73m^2; thus any subanalysis performed in this thesis using eGFRs greater than this is less robust. Additionally, more information regarding MI would also have been of benefit, specifically with regard to treatment of MI, degrees of rise in cardiac enzymes and details of any revascularisation. As acknowledged in each chapter, reliable smoking data and lipid studies would have been beneficial to this thesis.

One strength of the studies included in this thesis is the very long follow-up period, particularly when compared to other post-MI and HF studies. On the other hand, the long follow-up period makes it difficult to apply the finding of the studies to current patients who are benefiting from MI and HF therapies not available in the 1990s.

Finally, mortality data in these studies was very good, with excellent recording of all deaths. Coding of these deaths as being attributed to cardiovascular disease, cancer etc depended on analysis of death certificates; thus, this relies on the variable accuracy of general practitioners, junior doctors and procurator fiscals who complete the forms. The limitation of this method is highlighted by some "uncoded" deaths where no information was recorded on

the death certificate; whilst certainly unsatisfactory, the small numbers involved would have a negligible influence on overall results. Recording of other morbidity end points during the follow up period (such as further MI, hospital admissions, revascularisiation) would have very beneficial.

6.6 Suggestions for further studies

It is important to try to understand diseases processes in order to better target the development of treatments; research into cardiorenal disease is still at the information gathering stage and specific therapies are some way off. A number of different hypotheses have been raised in this thesis, and further studies, if designed correctly, could help in unravelling cardiorenal interaction. It may be of merit to study whether renal disease leads to more pronounced atherosclerosis in the absence of hypertension, DM or other cardiovascular risk factors; a simple animal model could be used, whereby total atherosclerotic burden could be measured and compared between subjects with and without induced renal impairment. Conversely, another study could look at renal function and change thereof in models with and without aggressive atherosclerosis. In either study, objective measurements of inflammation and RAAS activation could be undertaken.

Similar studies in humans would be more difficult due to ethical and practical considerations. Clearly, studies looking at individuals with renal impairment and aggressive cardiovascular disease would need to be observational. Furthermore, absolute atherosclerotic load in humans is very difficult to quantify, and repeated procedures attempting to measure this such as coronary angiography, CT angiography, carotid MRI and similar are expensive, time consuming and come with an inherent risk.

In terms of further population based studies, a study similar to those performed in the CRI could be designed to specifically investigate issues raised from thesis with regard to cardiorenal interaction. A large cohort of individuals would be recruited including some from the general population, some who had recently sustained a MI, some who had sustained a MI many some years previously and some with HF. A screening visit would allow the following: collation of information on medical history, medications, full information on MI including treatment and revascularisation; BP measurement; ECHO; urinanalysis and quantification of any proteinuria; blood sampling for BNP, inflammatory markers, serum creatinine, renin/aldosterone; ECG. A similar screening visit could be performed annually thereafter with further subsequent information gained on hospital admissions, BP and DM control. This study design clearly represents an expensive, time consuming process with many potential practical problems; however, it would generate a huge wealth of information on cardiorenal disease.

6.7 Conclusions

This thesis has demonstrated that mild to moderate renal impairment independently predicts adverse long term outcome in three different cohorts of the Glasgow population, thereby confirming results described in populations elsewhere. However, different definitions of renal impairment were needed in each cohort to demonstrate this, specifically with regard to serum creatinine cut-offs; eGFR and CKD classification failed to show an independent association with outcome in any cohort although eGFR quartiles predicted cardiovascular death in the GP-HF cohort. This thesis has also shown that in a post MI cohort, chronic change in renal function is a strong independent predictor of long term outcome, with a larger fall in renal

function particularly associated with cardiovascular death. Poorer renal function was associated with higher natriuretic peptide levels in both the post-MI cohort and GP-HF cohort and BNP was a strong independent predictor of outcome in these populations. Of note, elevated BNP following MI was associated with a larger subsequent fall in eGFR.

Cardiorenal interaction via hormonal, metabolic and haemodynamic processes clearly influences prognosis in a variety of different clinical settings, and this is most apparent in those with established cardiac or renal disease. Further study into the cardiorenal axis will improve our understanding of many disease processes, and may yield future therapies that will protect kidneys, prevent cardiovascular disease and ultimately prevent premature deaths.

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APPENDIX

FULL PUBLICATIONS GENERATED FROM THIS THESIS.

- "Declining renal function after myocardial infarction predicts poorer long-term outcome."

  C Aengus Murphy, Robin AP Weir, Stephen D Robb, Theresa A McDonagh, Henry J Dargie.

  Eur J Cardiovasc Prev Rehabil. 2009 Oct 13. [Epub ahead of print]

ABSTRACTS GENERATED FROM THIS THESIS

- "Chronic change in BNP after Myocardial Infarction adds no additional prognostic information over that gained from a once-off assessment of BNP."

  C Aengus Murphy, RAP Weir, SD Robb, TA McDonagh, HJ Dargie

  Moderated poster presentation, British Cardiovascular Society, 2010

- "Renal function and mortality in the Glasgow population."

  C Aengus Murphy, SD Robb, TA McDonagh, HJ Dargie

  Poster Presentation, European Society of Cardiology, Vienna 2007

- "The Influence of Renal Impairment and Changing Renal Function on Long Term Mortality Following Myocardial Infarction: A Glasgow Epidemiological Study."

  C Aengus Murphy, RIS Good, RAP Weir, SD Robb, TA McDonagh, HJ Dargie *Poster presentation, European Society of Cardiology, Munich, 2008*

- "Renal function and long term mortality in two cohorts of the Glasgow population."

  C Aengus Murphy, RIS Good, RAPWeir, SD Robb, TA McDonagh, HJ Dargie. *Oral Presentation, Scottish Cardiac Society 2007*

OTHER RELEVENT WORK PERFORMED DURING PRODUCTION OF THIS THESIS

Clinical Research Initiative

The ELDERLY cohort, which was the second large cohort study performed in the CRI project (see Figure 1.2) was also analysed during production of this thesis. As with the MONICA study, blood samples were only available for the rescreen visit performed in 1998 and data on symptoms, ECHO and medications were non-contemporaneous.

Results from this analysis were included in the ESC abstract of 2007 and SCS abstract of 2006. However, these results were not included in this thesis as they were thought to be of insufficient merit.

ATHENA

The Western Infirmary Glasgow has for many years run a specialist HF out-patient clinic, under the care of Professor Henry Dargie. Information gathered from this clinic includes weight, symptoms, ECHO and blood sampling for creatinine, BNP and haemoglobin concentrations. This data has been stored in the ATHENA database, based in the Clinical Research Initiative.

During the production of this thesis, analysis of the ATHENA database was performed with specific interest in change in renal function, weight and BNP concentrations. Work from this produced the following abstracts:

- "Change in renal function has little bearing on change in NT-BNP levels in patients with Heart Failure." CA Murphy, S Polymeros, S. Melcher, RAP Weir, HJ. Dargie. *Poster presentation. European Society of Cardiology Barcelona 2006*
- "Serial NT-proBNP in Heart Failure: the influence of changing haemoglobin, renal function and body weight over time." CA Murphy, S Polymeros, S Melcher, RAP Weir, HJ Dargie. *Poster Presentation ESC Heart Failure Congress, Stockholm 2007*